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# Ambient Water Quality Criteria for Lead

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# Ambient Water Quality Criteria for Lead

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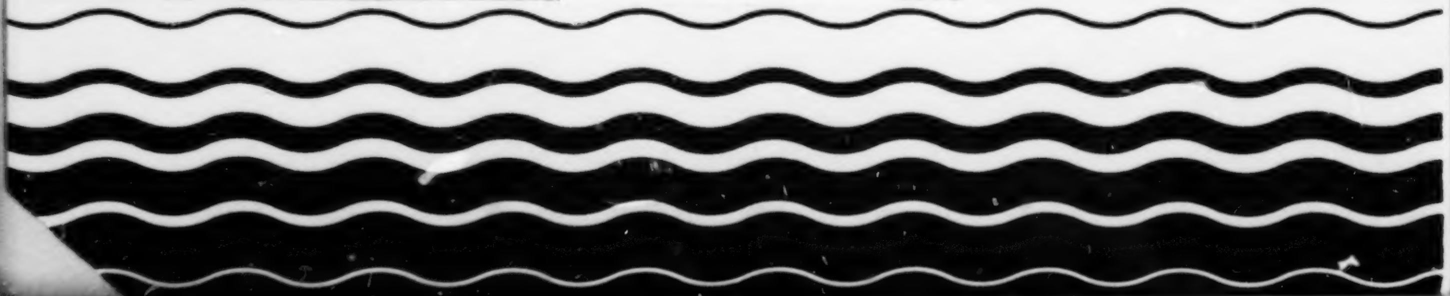

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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Lead. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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# AMBIENT WATER QUALITY CRITERIA FOR

# LEAD

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

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# FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

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Aquatic Life Toxicology:

Charles E. Stephan, ERL-Duluth
U.S. Environmental Protection Agency

John H. Gentile, ERL-Narragansett
U.S. Environmental Protection Agency

Mammalian Toxicology and Human Health Effects:

Paul B. Hammond (author)
University of Cincinnati

Michael L. Dourson (doc. mgr.) ECAO-Cin
U.S. Environmental Protection Agency

Jerry F. Stara (doc. mgr.) ECAO-Cin
U.S. Environmental Protection Agency

Patrick Durkin
Syracuse Research Corporation

W. Galke, ECAO-RTP
U.S. Environmental Protection Agency

Terri Laird, ECAO-Cin
U.S. Environmental Protection Agency

K. Mahaffey
U.S. Food and Drug Administration

Roy E. Albert*
Carcinogen Assessment Group
U.S. Environmental Protection Agency

R.J. Bull, HERL
U.S. Environmental Protection Agency

Thomas Clarkson
University of Rochester

Robert A. Ewing
Battelle - Columbus Laboratory

T.J. Haley
National Center for Toxicological Research

P. Landrigan
Center of Disease Control

H. Needleman
Children's Hospital Medical Center

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell, T. Highland, B. Gardiner.

*CAG Participating Members: Elizabeth L. Anderson, Larry Anderson, Dolph Arnicar, Steven Bayard, David L. Bayliss, Chao W. Chen, John R. Fowle III, Bernard Haberman, Charalingayya Hiremath, Chang S. Lao, Robert McGaughy, Jeffrey Rosenblatt, Dharm V. Singh, and Todd W. Thorslund.

# TABLE OF CONTENTS

Criteria Summary

Page

Introduction A-1

Aquatic Life Toxicology B-1
    Introduction B-1
    Effects B-2
        Acute Toxicity B-2
        Chronic Toxicity B-5
        Plant Effects B-8
        Residues B-9
        Miscellaneous B-9
        Summary B-11
    Criteria B-11
    References B-31

Mammalian Toxicology and Human Health Effects C-1
    Introduction C-1
    Exposure C-2
        Natural Background Levels C-2
        Man-generated Sources of Lead C-3
        Ingestion from Water C-3
        Ingestion from Food C-4
        Inhalation C-9
        Dermal C-9
        Miscellaneous Sources C-9
    Pharmacokinetics C-15
        Absorption C-16
        Dermal C-19
        Distribution C-19
        Metabolism C-21
        Excretion C-21
        Contributions of Lead from Diet versus Air to PbB C-22
    Effects C-35
        Carcinogenicity C-48
        Teratogenicity C-63
        Mutagenicity C-66
        Reproductive Effects C-66
        Renal Effects C-68
        Cardiovascular Effects C-70
        Miscellaneous Effects C-71
    Criterion Formulation C-72
        Existing Guidelines and Standards C-72
        Current Levels of Exposure C-72
        Special Groups at RIsk C-73
        Basis and Derivation of Criterion C-73
    References C-81
Appendix C-104

# CRITERIA DOCUMENT

# LEAD

## CRITERIA

### Aquatic Life

For total recoverable lead, the criterion (in μg/l) to protect freshwater aquatic life as derived using the Guidelines, is the numerical value given by $e^{(2.35[\ln(\text{hardness})]-9.48)}$ as a 24-hour average and the concentration (in μg/l) should not exceed the numerical value given by $e^{(1.22[\ln(\text{hardness})]-0.47)}$ at any time. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$ the criteria are 0.75, 3.8, and 20 μg/l, respectively, as 24-hour averages, and the concentrations should not exceed 74, 170, and 400 μg/l, respectively, at any time.

The available data for total recoverable lead indicate that acute and chronic toxicity to saltwater aquatic life occur at concentrations as low as 668 and 25 μg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

### Human Health

The ambient water quality criterion for lead is recommended to be identical to the existing water standard which is 50 μg/l. Analysis of the toxic effects data resulted in a calculated level which is protective of human health against the ingestion of contaminated water and contaminated aquatic organisms. The calculated value is comparable to the present standard. For this reason a selective criterion based on exposure solely from consumption of 6.5 grams of aquatic organisms was not derived.

# INTRODUCTION

Lead (atomic weight 207.2) is a soft gray, acid-soluble metal (Windholz, 1976) and exists in three oxidation states, 0, +2, and +4. Lead is a major constituent of more than 200 identified minerals. Most of these are rare, and only three are found in sufficient abundance to form mineral deposits: galena (PbS) the simple sulfide, angelesite ($PbSO_4$) the sulfate, and cerrusite ($PbCO_3$) the carbonate (U.S. EPA, 1979). Lead is used in electroplating, metallurgy, and the manufacture of construction materials, radiation protective devices, plastics, and electronics equipment.

Although neither metallic lead nor the common lead minerals are classified as soluble in water, they can both be solubilized by some acids; in contrast, some of the lead compounds produced industrially are considered water soluble. Natural lead compounds are not usually mobile in normal ground or surface water because the lead leached from ores becomes adsorbed by ferric hydroxide or tends to combine with carbonate or sulfate ions to form insoluble compounds (Hem, 1976). The solubility of lead compounds in water depends heavily on pH and ranges from about 10,000,000 µg/l of lead at pH 5.5 to 1 µg/l at pH 9.0 (Hem and Durum, 1973). Lead does reach the aquatic environment through precipitation, fallout of lead dust, street runoff, and both industrial and municipal wastewater discharges (U.S. EPA, 1976). Inorganic lead compounds are most stable in the plus two valence state, while organolead compounds are more stable in the plus four state (Standen, 1967).

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## Aquatic Life Toxicology*

## INTRODUCTION

The acute and chronic adverse effects of lead have been studied with a variety of freshwater organisms. Representative test animals listed in Tables 1 through 6 include fish from six different families (Salmonidae, Cyprinidae, Catostomidas, Ictaluridae, Poeciliidae, and Centrarchidae), and invertebrate species from the nine groups (rotifers, annelids, snails, cladocerans, copepods, isopods, mayflies, stoneflies, and caddisflies). Toxicity tests have also been conducted with freshwater plants from the algal, desmid and diatom groups, and both fish and invertebrate species have been used in bioconcentration tests.

Acute toxicity tests have been conducted with lead and a variety of saltwater invertebrates, but no tests with fish are available. Results indicate a range of acute values from 668 µg/l for a copepod to 27,000 µg/l for the adult soft shell clam. A chronic test has been conducted with one invertebrate species, the mysid shrimp, and the chronic value was 25 µg/l. Select invertebrate and algal species are good accumulators of lead. Bioconcentration factors calculated on a wet weight basis ranged from 17.5 for the hard clam to 2,570 for the mussel.

Of the analytical measurements currently available, a water quality criterion for lead is probably best stated in terms of total recoverable lead, because of the variety of forms of lead that can exist in bodies of water and the various chemical and toxicological properties of these forms. The forms of lead that are commonly found in bodies of water and are not measured by the total recoverable procedure, such as the lead that is a part of minerals, clays and sand, probably are forms that are less toxic to aquatic life and probably will not be converted to the more toxic forms very readily under natural conditions. On the other hand, forms of lead that are commonly found in bodies of water and are measured by the total recoverable procedure, such as the free ion, and the hydroxide, carbonate, and sulfate salts, probably are forms that are more toxic to aquatic life or can be converted to the more toxic forms under natural conditions.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Because the criterion is derived on the basis of tests conducted on soluble inorganic salts of lead, the total and total recoverable lead concentrations in the tests will probably be about the same, and a variety of analytical procedures will produce about the same results. Except as noted, all concentrations reported herein are expected to be essentially equivalent to total recoverable lead concentrations. All concentrations are expressed as lead, not as the compound tested.

## EFFECTS

### Acute Toxicity

Table 1 contains six acute values for three freshwater invertebrate species. Only one of the tests was flow-through (Spehar, et al. 1978) but in two, the toxicant concentrations were measured (Spehar, et al. 1978; Chapman, et al. Manuscript). Acute tests were conducted at three different levels of water hardness with *Daphnia magna* (Chapman, et al. Manuscript), demonstrating that daphnids were three times more sensitive to lead in soft water than in hard water. This acute value for *Daphnia magna* in soft water agrees closely with the value reported earlier for the same species in soft water by Biesinger and Christensen (1972). Rotifers tested for 96 hours in soft water by Buikema, et al. (1974) were very resistant to lead; however, scuds were reported by Spehar, et al. (1978) to be more sensitive to lead than any other invertebrate thus far tested. Interestingly, this same relationship existed in longer exposures lasting up to 28 days in which the scud was far more sensitive to lead than a snail, cladoceran, chironomid, mayfly, stonefly, and caddisfly (Table 6) (Spehar, et al. 1978; Biesinger and Christensen, 1972; Anderson, et al. 1980; and Nehring, 1976).

Thirteen acute toxicity tests have been conducted on lead with six species of fish (Table 1). Of the 13 only three were reported to be flow-through, and measured toxicant concentrations were reported for only one (Holcombe, et al. 1976). The results of acute tests conducted by Davies, et al. (1976) with rainbow trout in hard water are reported as unmeasured values in Table 1, because total lead concentrations were not measured, even though the dissolved lead concentrations were.

The data in Table 1 indicate a relationship between water hardness and the acute toxicity of lead to rainbow trout (Davies, et al. 1976), fathead minnows and bluegills (Pickering and Henderson, 1966), because lead was generally much more toxic in soft water. Another example of the effect of hardness was reported by Tarzwell and Henderson (1960) who conducted 96-hour exposures of fathead minnows to lead in soft and hard water (20 and 400 mg/l as $CaCO_3$, respectively). Results from the soft water test are shown in Table 1. The hard water exposure is included in Table 6 because an $LC_{50}$ value was not obtained within 96 hours; however, this test did show that the hard water $LC_{50}$ value was greater than 75,000 µg/l which meant that the $LC_{50}$ in hard water was at least 31 times that in soft water. Hale (1977) conducted an acute exposure of rainbow trout to lead and obtained an $LC_{50}$ value of 8,000 µg/l. This value is six times greater than the $LC_{50}$ value obtained for rainbow trout in soft water by Davies, et al. (1976). Hale did not report water hardness; however, alkalinity and pH were reported to be 105 mg/l and 7.3, respectively, which suggests that this water was probably harder than the soft test water used by Davies, et al. (1976). Wallen, et al. (1957) also reported high acute lead values for the mosquitofish; however, these authors also did not report water hardness and the test was conducted in turbid water contining suspended clay particles at apporoximately 300,000 µg/l (Table 6). Pickering and Henderson (1966) found that lead acetate was about as toxic as lead chloride to the fathead minnow in soft water (Tables 1 and 6).

An exponential equation was used to describe the observed relationship of the acute toxicity of lead to hardness in fresh water. A least squares regression of the natural logarithms of the acute values on the natural logarithms of hardness produced slopes of 1.05, 2,48, 1.60, and 1.01, respectively, for Daphnia magna, rainbow trout, fathead minnow, and bluegill (Table 1). The slope for Daphnia magna was significant, but that for rainbow trout was not. The slopes for the bluegill and fathead minnow were based on data for two hardnesses each, although four tests are available with the minnow. An arithmetic mean slope of 1.22 was calculated for the three species other than the rainbow trout. This mean slope was used with the geometric mean toxicity value and hardness for each species to obtain a logarithmic intercept for each of the nine freshwater species for which acute values are available for lead.

The species mean intercept, calculated as the exponential of the logarithmic intercept, was used to compare the relative acute sensitivities (Table 3). The Guidelines specify that in order to derive a criterion the minimum data base should include at least one acute value for a benthic insect. No such value is available for lead. However, 7- to 28-day soft water exposures of the mayfly, stonefly, and caddisfly to lead have been reported by Nehring (1976), Warnick and Bell (1969), and Spehar, et al. (1978) (Table 6). Their results indicate that benthic insects are rather insensitive to lead. Although the data are not really comparable, it appears that the caddisfly may be the least sensitive of the three and may be slightly less sensitive than the goldfish. In an attempt to account in some way for these insensitive species in the derivation of the Final Acute Intercept, a caddisfly was entered as the least sensitive species in the list of freshwater intercepts in Table 3.

A freshwater Final Acute Intercept of 0.623 μg/l was obtained for lead using the species mean intercepts listed in Table 3 and the calculation procedures described in the Guidelines. Thus the Final Acute Equation is $e^{(1.22[\ln(\text{hardness})]-0.47)}$.

No standard acute toxicity values for saltwater fish species are available but several are available for invertebrate species. The most sensitive invertebrate species was a copepod *Acartia clausi* with an $LC_{50}$ of 668 μg/l and the least sensitive was the soft shell clam *Mya arenaria* with an $LC_{50}$ of 27,000. A value of 2,450 was obtained with oyster larvae *Crassostrea virginica* in a static test and a $LC_{50}$ of 2,960 was recorded for mysid shrimp *Mysidopsis bahia* in a flow-through test in which concentrations were measured (Table 1). Acute values are not available for enough appropriate kinds of species to allow calculation of a Saltwater Final Acute Value.

## Chronic Toxicity

Four tests of the chronic toxicity of lead to freshwater invertebrate species have been conducted (Table 2). Chapman, et al. (Manuscript) studied the chronic toxicity of lead to *Daphnia magna* at three different hardnesses. Results shown in Table 2 demonstrate that daphnids were nearly 11 times more sensitive to lead in the soft water. For the same species in a different soft water, a chronic value over four times higher (Table 6) was obtained by Biesinger and Christensen (1972) in a test in which the concentrations of lead were not measured. Use of the comparable acute value of 450 µg/l (Table 1) results in an acute-chronic ratio of 8.2.

A life cycle test on lead in hard water was conducted by Borgmann, et al. (1978) with snails. These authors used biomass as their endpoint and reported that lead concentrations as low as 19 µg/l significantly decreased survival but not growth or reproduction. After a thorough review of this work, however, it was not at all clear how these investigators arrived at such a low effect concentration. This publication did, however, contain suitable information for determining a chronic value. Chronic limits were taken directly from the cumulative percent survival figure which showed no observed effect on survival at 12 µg/l and almost complete mortality at 54 µg/l. The chronic value for snails shown in Table 2 was therefore established at 25 µg/l, which is somewhat lower than the chronic value reported for daphnids in hard water.

Seven chronic tests on lead have been conducted with six species of freshwater fish (Table 2), all of which were in soft water. In addition, Davies, et al. (1976) described the long-term effects on rainbow trout fry and fingerlings exposed to various concentrations of lead for 19 months in hard and soft water (Table 6). Although these experiments were neither life cycle (no natural reproduction) nor early life stage (no embryos exposed), they do provide valuable information concerning the relationship between water hardness and chronic lead toxicity to fish. During these 19-month exposures, most of the trout (60 to 100 percent) developed spinal deformities in hard water at measured lead concentrations of 850 µg/l and above.

However, during the soft water exposure most trout (44 to 97 percent) developed spinal deformities in measured lead concentrations as low as 31 µg/l (Table 6). These results strongly demonstrate that lead is more chronically toxic in soft water than in hard water.

Davies, et al. (1976) also published results of an early life stage test with rainbow trout in soft water (Table 2). Even through this test was started with embryos and continued for 19 months after hatch, it could not be considered a life cycle test because no reproduction occurred. The chronic limits that these authors chose were somewhat lower than those shown in Table 2, because they based their results on a very low incidence of black colored tails and spinal deformities (0.7 and 4.7 percent, respectively). Because this test was not conducted with duplicate exposures, statistically significant differences could not be determined. After careful examination of their results it was decided that the chronic limits (Table 2) should be established on the occurrence of spinal curvatures only and at lead concentrations which caused a substantial increase in these deformities. Even though the incidence of black tail was apparently related to the concentration of lead, it could not by itself be considered an important adverse effect.

Spinal deformities have also been cause by lead in a life cycle test with brook trout (Holcombe, et al. 1976) and in early life stage tests with rainbow trout, northern pike and walleye (Sauter, et al. 1976). On the other hand, Sauter, et al. (1976) did not observe deformities during early life stage tests with lake trout, channel catfish, white sucker, and bluegill. Results of tests by Sauter, et al. (1976) with northern pike and walleye, however, were not included in Tables 2 and 6 because of excessive mortality due to cannibalism and feeding problems. The chronic value obtained for rainbow trout by Sauter, et al. (1976) is somewhat higher than that chronic value derived from Davies, et al. (1976). Even though the hardnesses were about the same, differences could be due to differences in the length of exposure (2 months vs. 19 months).

As was done with the freshwater acute values, the freshwater chronic values of Chapman, et al. (Manuscript) were regressed against hardness to account for the apparent effect of hardness on the chronic toxicity of lead and a slope of 2.35 was obtained. Even though this slope is not significant because it is based on only three values, it relects the obvious effect of hardness on chronic toxicity. In the same manner as for acute toxicity, the chronic slope was used with the geometric mean chronic toxicity value and hardness for each species to obtain a logarithmic intercept and a species mean chronic intercept for each species for which a chronic value is available (Table 2). A Freshwater Final Chronic Intercept of 0.000076 µg/l was then obtained using the calculation procedures described in the Guidelines. Thus, the Final Chronic Equation is $e^{(2.35[\ln(\text{hardness})]-9.48)}$.

The mysid shrimp *Mysidopsis bahia* is the only saltwater species with which a chronic test has been conducted on lead (Table 2). The most sensitive observed adverse effect was reduced spawning (U.S. EPA, 1980) and the resulting chronic value was 25 µg/l. The 96-hour $LC_{50}$ for this same species in the same study was 2,960 µg/l, producing an acute-chronic ratio of 119.

## Plant Effects

Four static tests on three species of algae have been reported by Monahan (1976) (Table 4). These exposures were conducted for 7 days and concentrations of lead were not measured. Results of short exposures of algae and diatoms to unmeasured lead concentrations have also been published by Malanchuk and Gruendling (1973) (Table 6). The adverse effect concentrations from these tests ranged from 500 to 28,000 µg/l. It would appear therefore that any adverse effects of lead on plants are unlikely at concentrations protective of chronic effects on freshwater animals.

No saltwater plant species have been exposed to inorganic lead, but one saltwater algal species Dunaliella tertiolecta has been exposed to both tetramethyl and tetraethyl lead. The results (Table 6) demonstrate that this species is more sensitive to tetraethyl lead by a factor greater than 10. No data are available concerning the relative toxicities of inorganic lead and these organolead compounds.

## Residues

Four freshwater invertebrate species have been exposed to lead (Borgmann, et al. 1978; Spehar, et al. 1978) and the bioconcentration factors ranged from 499 to 1,700 (Table 5). Brook trout and bluegills were also exposed to lead (Holcombe, et al. 1976, and Atchison, et al. 1977) and calculated bioconcentration factors were 42 and 45, respectively (Table 5).

Some species of saltwater bivalve molluscs, diatoms and phytoplankton are capable of accumulating lead (Table 5). The bioconcentration factors range from 17.5 with the hard clam to 2,570 with the mussel. Because the duration of the study may be an important consideration in bioconcentration studies, this comparison is not entirely valid since the mussel was exposed for 130 days and the hard clam for only 56 days.

Neither a freshwater nor a saltwater Final Residue Value can be calculated because no maximum permissible tissue concentration is available for lead.

## Miscellaneous

Many of the values in Table 6 have already been discussed. Spehar (1978) found no adverse effects on a freshwater snail, scud, stonefly, and caddisfly in 28 days at 565 µg/l. Pickering and Henderson (1966) found that lead chloride and lead acetate are about equally toxic to fathead minnows in static tests in soft water (Table 1 and 6), but Wallen, et al. (1957) found that lead oxide is much less acutely toxic than lead nitrate to the mosquitofish in turbid water.

The 10-day test conducted by Anderson, et al. (1980) (Table 6) showed that the midge, *Tanytarsus dissimilis*, is rather insensitive to lead with a chronic value of 258 µg/l. This test included exposure of the species during most of its life cycle and several of the presumably sensitive molts, and so should probably be considered as useful as the early life stage test with fish.

A variety of other effects on saltwater organisms have been observed. Gray and Ventilla (1973) observed a reduction in growth rate in a ciliate protozoan after a 12 hour exposure to a lead concentration of 150 µg/l. Woolery and Lewin (1976) observed a reduction in photosynthesis and respiration in the diatom *Pheodactylum tricornutum* at concentrations of lead ranging from 100 to 10,000 µg/l. However, Hannan and Patouillet (1972) obtained no growth inhibition with *P. tricornutum* at a concentration of 1,000 µg/l after 72 hours. Rivkin (1979) using growth rate to determine toxicity to the diatom, *Skeletonema costatum*, reported a 12 day $EC_{50}$ of 5.1 µg/l. Hessler (1974) observed delayed cell division in the phytoplankton, *Platymonas subcordiformus*, after treatment with 2,500 µg/l for 72 hours. At 60,000 µg/l, Hessler (1974) reported not only growth retardation but also death. Benijts-Claus and Benijts (1975) observed delayed larval development in the mud crab, *Rhithropanopeus harrisii*, after treatment with lead concentrations of 50 µg/l. In *Fundulus heteroclitus*, Weis and Weis (1977) observed depressed axis formation in developing embryos with lead concentrations of 100 µg/l. Reish and Carr (1978), found that 1,000 µg/l suppressed reproduction of two polychaete species, *Ctenodriluis serratus* and *Ophryotrocha disdema*, in a 21-day test.

## Summary

Standard acute data for lead are available for nine freshwater fish and invertebrate species with a range from 124 to 542,000 μg/l. Chronic tests have been conducted with two invertebrate species and six fish species with the chronic values ranging from 12 to 174 μg/l. Both the acute and chronic toxicities of lead to freshwater animals decrease as hardness increases.

Freshwater algae are affected by concentrations of lead above 500 μg/l, based on data for three species. Bioconcentration factors ranging from 42 to 1,700 are available for four invertebrate and two fish species.

Acute values for five saltwater species ranged from 668 μg/l for a copepod to 27,000 μg/l for the soft shell clam. A chronic toxicity test was conducted for the mysid shrimp and adverse effects were observed at 37 μg/l but not at 17 μg/l. The acute-chronic ratio for this species is 118.

Delayed embryonic development, suppressed reproduction and inhibition of growth rate among fish, crab, polychaete worm, and plankton were also caused by lead.

## CRITERIA

For total recoverable lead the criterion (in μg/l) to protect freshwater aquatic life as derived using the Guidelines is the numerical value given by $e^{(2.35[\ln(\text{hardness})]-9.48)}$ as a 24-hour average and the concentration (in μg/l) should not exceed the numerical value given by $e^{(1.22[\ln(\text{hardness})]-0.47)}$ at any time. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$ the criteria are 0.75, 3.8, and 20 μg/l, respectively, as 24-hour averages, and the concentrations should not exceed 74, 170, and 400 μg/l, respectively, at any time.

The available data for total recoverable lead indicate that acute and chronic toxicity to saltwater aquatic life occur at concentrations as low as 668 and 25 µg/l, respectively, and would occur at lower concentrations among species that are more sensitive than those tested.

Table 1. Acute values for lead

| Species | Method* | Chemical | Hardness (mg/l as $CaCO_3$) | LC50/EC50** (µg/l) | Species Mean Acute Value** (µg/l | Reference |
|---|---|---|---|---|---|---|
| | | | FRESHWATER SPECIES | | | |
| Rotifer, *Philodina acuticornis* | S, U | Lead chloride | 25 | 40,800 | - | Buikema, et al. 1974 |
| Cladoceran, *Daphnia magna* | S, U | Lead chloride | 45 | 450 | - | Biesinger & Christensen, 1972 |
| Cladoceran, *Daphnia magna* | R, M | Lead nitrate | 54 | 612 | - | Chapman, et al. Manuscript |
| Cladoceran, *Daphnia magna* | R, M | Lead nitrate | 110 | 952 | - | Chapman, et al. Manuscript |
| Cladoceran, *Daphnia magna* | R, M | Lead nitrate | 152 | 1,910 | - | Chapman, et al. Manuscript |
| Scud, *Gammarus pseudolimnaeus* | FT, M | Lead nitrate | 46 | 124 | - | Spehar, et al. 1978 |
| Rainbow trout, *Salmo gairdneri* | S, U | Lead nitrate | 290 | 542,000 | - | Davies, et al. 1976 |
| Rainbow trout, *Salmo gairdneri* | S, U | Lead nitrate | 353 | 471,000 | - | Davies, et al. 1976 |
| Rainbow trout, *Salmo gairdneri* | FT, U | Lead nitrate | 28 | 1,170 | - | Davies, et al. 1976 |
| Rainbow trout (2 mos), *Salmo gairdneri* | FT, U | Lead nitrate | - | 8,000 | - | Hale, 1977 |
| Brook trout (18 mos), *Salvelinus fontinalis* | FT, M | Lead nitrate | 44 | 4,100 | - | Holcombe, et al. 1976 |
| Fathead minnow, *Pimephales promelas* | S, U | Lead chloride | 20 | 2,400 | - | Tarzwell & Henderson, 1960 |
| Fathead minnow, *Pimephales promelas* | S, U | Lead chloride | 20 | 5,580 | - | Pickering & Henderson, 1966 |
| Fathead minnow, *Pimephales promelas* | S, U | Lead chloride | 20 | 7,330 | - | Pickering & Henderson, 1966 |

Table 1. (Continued)

| Species | Method* | Chemical | Hardness (mg/l as $CaCO_3$) | LC50/EC50** (µg/l) | Species Mean Acute Value** (µg/l | Reference |
|---|---|---|---|---|---|---|
| Fathead minnow, *Pimephales promelas* | S, U | Lead chloride | 360 | 482,000 | - | Pickering & Henderson, 1966 |
| Goldfish, *Carassius auratus* | S, U | Lead chloride | 20 | 31,500 | - | Pickering & Henderson, 1966 |
| Guppy (6 mos), *Poecilia reticulata* | S, U | Lead chloride | 20 | 20,600 | - | Pickering & Henderson, 1966 |
| Bluegill, *Lepomis macrochirus* | S, U | Lead chloride | 20 | 23,800 | - | Pickering & Henderson, 1966 |
| Bluegill, *Lepomis macrochirus* | S, U | Lead chloride | 360 | 442,000 | - | Pickering & Henderson, 1966 |
| | | | SALTWATER SPECIES | | | |
| Oyster, *Crassostrea virginica* | S, U | Lead nitrate | - | 2,450 | 2,450 | Calabrese, et al. 1973 |
| Hard clam, *Mercenaria mercenaria* | S, U | Lead nitrate | - | 780 | 780 | Calabrese & Nelson, 1974 |
| Soft shell clam (adult), *Mya arenaria* | S, U | Lead nitrate | - | 27,000 | 27,000 | Eisler, 1977 |
| Mysid shrimp, *Mysidopsis bahia* | FT, M | Lead nitrate | - | 2,960 | 2,960 | U.S. EPA, 1980 |
| Copepod, *Acartia clausi* | S, U | Lead nitrate | - | 668 | 668 | U.S. EPA, 1980 |

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* S = static, R = renewal, FT = flow-through, M = measured, U = unmeasured

**Results are expressed as lead, not as the compound.

**Table 1. (Continued)**

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Freshwater

Acute toxicity vs. hardness

*Daphnia magna*: slope = 1.05, intercept = 2.13, r = 0.97, p = 0.05, n = 4

Rainbow trout: slope = 2.48, intercept = -1.16, r = 0.99, not significant, n = 3

Fathead minnow: slope = 1.60, intercept = 3.62, r = 0.98, p = 0.05, n = 4

Bluegill: slope = 1.01, intercept = 7.05, r = 1.00, n = 2

Arithmetic mean acute slope = 1.22 (slope for rainbow trout not used)

## Table 2. Chronic values for lead

| Species | Test* | Chemical | Hardness (mg/l as $CaCO_3$) | Limits (µg/l) | Chronic Value** (µg/l) | Reference |
|---|---|---|---|---|---|---|
| | | | FRESHWATER SPECIES | | | |
| Cladoceran, *Daphnia magna* | LC | Lead nitrate | 52 | 9-17 | 12 | Chapman, et al. Manuscript |
| Cladoceran, *Daphnia magna* | LC | Lead nitrate | 102 | 78-181 | 119 | Chapman, et al. Manuscript |
| Cladoceran, *Daphnia magna* | LC | Lead nitrate | 151 | 85-193 | 128 | Chapman, et al. Manuscript |
| Snail, *Lymnea palustris* | LC | Lead nitrate | 139 | 12-54 | 25 | Borgmann, et al. 1978 |
| Rainbow trout, *Salmo gairdneri* | ELS | Lead nitrate | 28 | 13-27 | 19 | Davies, et al. 1976 |
| Rainbow trout, *Salmo gairdneri* | ELS | Lead nitrate | 35 | 71-146 | 102 | Sauter, et al. 1976 |
| Brook trout, *Salvelinus fontinalis* | LC | Lead nitrate | 44 | 58-119 | 83 | Holcombe, et al. 1976 |
| Lake trout, *Salvelinus namaycush* | ELS | Lead nitrate | 33 | 48-83 | 63 | Sauter, et al. 1976 |
| Channel catfish, *Ictalurus punctatus* | ELS | Lead nitrate | 36 | 75-136 | 101 | Sauter, et al. 1976 |
| White sucker, *Catostomus commersoni* | ELS | Lead nitrate | 38 | 119-253 | 174 | Sauter, et al. 1976 |
| Bluegill, *Lepomis macrochirus* | ELS | Lead nitrate | 41 | 70-120 | 92 | Sauter, et al. 1976 |
| | | | SALTWATER SPECIES | | | |
| Mysid shrimp, *Mysidopsis bahia* | LC | Lead nitrate | - | 17-37 | 25 | U.S. EPA, 1980 |

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* LC = life cycle or partial life cycle, ELS = early life stage

**Results are expressed as lead, not as the compound.

**Table 2. (Continued)**

Freshwater

Chronic toxicity vs. hardness

*Daphnia magna*: slope = 2.35, intercept = -6.60, r = 0.94, not significant, n = 3

Chronic slope = 2.35 (see text)

Acute-Chronic Ratios

| Species | Acute Value (µg/l) | Chronic Value (µg/l) | Ratio |
|---|---|---|---|
| Cladoceran, *Daphnia magna* | 612 | 12 | 51 |
| Cladoceran, *Daphnia magna* | 952 | 119 | 8 |
| Cladoceran, *Daphnia magna* | 1,910 | 128 | 15 |
| Rainbow trout, *Salmo gairdneri* | 1,170 | 19 | 62 |
| Brook trout, *Salvelinus fontinalis* | 4,100 | 83 | 49 |
| Bluegill, *Lepomis macrochirus* | 23,800 | 92 | 259 |
| Mysid shrimp, *Mysidopsis bahia* | 2,960 | 25 | 118 |

**Table 2. (Continued)**

| Rank* | Species | Species Mean Chronic Intercept (µg/l) |
|---|---|---|
| 8 | White sucker,<br>*Catostomus commersoni* | 0.034 |
| 7 | Channel catfish,<br>*Ictalurus punctatus* | 0.022 |
| 6 | Lake trout,<br>*Salvelinus namaycush* | 0.017 |
| 5 | Bluegill,<br>*Lepomis macrochirus* | 0.015 |
| 4 | Rainbow trout,<br>*Salmo gairdneri* | 0.013 |
| 3 | Brook trout,<br>*Salvelinus fontinalis* | 0.011 |
| 2 | Cladoceran,<br>*Daphnia magna* | 0.0013 |
| 1 | Snail,<br>*Lymnea palustris* | 0.00023 |

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* Ranked from least sensitive to most sensitive based on species mean chronic intercept.

Freshwater

Final Chronic Intercept = 0.000076 µg/l

Natural logarithm of 0.000076 = -9.48

Chronic slope = 2.35

Final Chronic Equation = $e^{(2.35[\ln(\text{hardness})]-9.48)}$

Table 3. Species mean acute intercepts and values and acute-chronic ratios for lead

| Rank* | Species | Species Mean Acute Intercept (µg/l) | Species Mean Acute-Chronic Ratio |
|---|---|---|---|
| | | FRESHWATER SPECIES | |
| 10 | Caddisfly,**<br>(unspecified) | - | - |
| 9 | Goldfish,<br>Carassius auratus | 815 | - |
| 8 | Rotifer,<br>Philodina acuticornis | 804 | - |
| 7 | Guppy,<br>Poecilia reticulata | 533 | - |
| 6 | Bluegill,<br>Lepomis macrochirus | 455 | 259 |
| 5 | Fathead minnow,<br>Pimephales promelas | 158 | - |
| 4 | Rainbow trout,<br>Salmo gairdneri | 158 | 62 |
| 3 | Brook trout,<br>Salvelinus fontinalis | 40.5 | 49 |
| 2 | Cladoceran,<br>Daphnia magna | 4.02 | 18 |
| 1 | Scud,<br>Gammarus pseudolimnaeus | 1.16 | - |

Table 3. (Continued)

| Rank* | Species | Species Mean Acute Value (µg/l) | Species Mean Acute-Chronic Ratio |
|---|---|---|---|
| | SALTWATER SPECIES | | |
| 5 | Soft shell clam, *Mya arenaria* | 27,000 | - |
| 4 | Mysid shrimp, *Mysidopsis bahia* | 2,960 | 118 |
| 3 | Oyster, *Crassostrea virginica* | 2,450 | - |
| 2 | Hard clam, *Mercenaria mercenaria* | 780 | - |
| 1 | Copepod, *Acartia clausii* | 668 | - |

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* Ranked from least sensitive to most sensitive based on species mean acute intercept or value.

** See text.

Freshwater

Final Acute Intercept = 0.623 µg/l

Natural logarithm of 0.623 = -0.47

Acute slope = 1.22 (see Table 1)

Final Acute Equation = $e^{(1.22[\ln(\mathrm{hardness})]-0.47)}$

## Table 4. Plant values for lead

| Species | Chemical | Hardness (mg/l as $CaCO_3$) | Effect | Result* (µg/l) | Reference |
|---|---|---|---|---|---|
| FRESHWATER SPECIES | | | | | |
| Alga, *Ankistrodesmus* sp. | Lead chloride | - | 24% growth inhibition | 1,000 | Monahan, 1976 |
| Alga, *Chlorella* sp. | Lead chloride | - | 53% growth inhibition | 500 | Monahan, 1976 |
| Alga, *Scenedesmus* sp. | Lead chloride | - | 35% growth inhibition | 500 | Monahan, 1976 |
| Alga, *Selenastrum* sp. | Lead chloride | - | 52% growth inhibition | 500 | Monahan, 1976 |

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* Results are expressed as lead, not as the compound. All results are based on unmeasured concentrations.

## Table 5. Residues for lead

| Species | Tissue | Chemical | Bioconcentration Factor | Duration (days) | Reference |
|---|---|---|---|---|---|
| | | FRESHWATER SPECIES | | | |
| Snail, *Lymnea palustris* | Whole body | Lead nitrate | 1,700* | 120 | Borgmann, et al. 1978 |
| Snail, *Physa integra* | Whole body | Lead nitrate | 738* | 28 | Spehar, et al. 1978 |
| Stonefly, *Pteronarcys dorsata* | Whole body | Lead nitrate | 1,120* | 28 | Spehar, et al. 1978 |
| Caddisfly, *Brachycentrus* sp. | Whole body | Lead nitrate | 499* | 28 | Spehar, et al. 1978 |
| Brook trout (embryo-3 mos), *Salvelinus fontinalis* | Whole body | Lead nitrate | 42* | 140 | Holcombe, et al. 1976 |
| Bluegill, *Lepomis macrochirus* | Whole body | - | 45* | -** | Atchison, et al. 1977 |
| | | SALTWATER SPECIES | | | |
| Oyster, *Crassostrea virginica* | Soft parts | Lead nitrate | 536 | 140 | Zaroogian, et al. 1979 |
| Oyster, *Crassostrea virginica* | Soft parts | Lead nitrate | 68* | 49 | Pringle, et al. 1968 |
| Oyster, *Crassostrea virginica* | Soft parts | Lead nitrate | 1,400 | 70 | Shuster & Pringle, 1969 |
| Quahaug, hard clam, *Mercenaria mercenaria* | Soft parts | Lead nitrate | 17.5* | 56 | Pringle, et al. 1968 |
| Soft shell clam, *Mya arenaria* | Soft parts | Lead nitrate | 112* | 70 | Pringle, et al. 1968 |
| Mussel, *Mytilus edulis* | Soft parts | Lead nitrate | 650* | 40 | Schulz-Baldes, 1974 |
| Mussel, *Mytilus edulis* | Soft parts | Lead chloride | 200* | 37 | Talbot, et al. 1976 |

**Table 5. (Continued)**

| Species | Tissue | Chemical | Bioconcentration Factor | Duration (days) | Reference |
|---|---|---|---|---|---|
| Mussel,<br>*Mytilus edulis* | Soft parts | Lead nitrate | 2,570* | 130 | Schulz-Baldes, 1972 |
| Mussel,<br>*Mytilus edulis* | Soft parts | Lead nitrate | 2,080* | 130 | Schulz-Baldes, 1972 |
| Mussel,<br>*Mytilus edulis* | Soft parts | Lead nitrate | 796* | 130 | Schulz-Baldes, 1972 |
| Diatom,<br>*Phaeodactylum tricornutum* | Whole body | Lead chloride | 1,050* | 1/24 | Schulz-Baldes, 1976 |
| Diatom,<br>*Ditylum brightwellii* | Cells | Lead chloride | 725* | 14 | Canterford, et al, 1978 |
| Phytoplankton,<br>*Platymonas subcordiformis* | Whole body | Lead chloride | 933* | 1/24 | Schulz-Baldes, 1976 |

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* Bioconcentration factors have been converted from dry weight to wet weight.

**This field study was conducted with a natural population of bluegills living in a small lake which was extensively analyzed for lead, zinc and cadmium.

### Table 6. Other data for lead

| Species | Chemical | Hardness (mg/l as $CaCO_3$) | Duration | Effect | Result* (µg/l) | Reference |
|---|---|---|---|---|---|---|
| | | | FRESHWATER SPECIES | | | |
| Alga, *Anabaena* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 15,000 | Malanchuk & Gruendling, 1973 |
| Alga, *Anabaena* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 26,000 | Malanchuk & Gruendling, 1973 |
| Alga, *Anabaena* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 15,000 | Malanchuk & Gruendling, 1973 |
| Alga, *Chlamydomonas* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 17,000 | Malanchuk & Gruendling, 1973 |
| Alga, *Chlamydomonas* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 17,000 | Malanchuk & Gruendling, 1973 |
| Desmid, *Cosmarium* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 5,000 | Malanchuk & Gruendling, 1973 |
| Desmid, *Cosmarium* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 5,000 | Malanchuk & Gruendling, 1973 |
| Desmid, *Cosmarium* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 5,000 | Malanchuk & Gruendling, 1973 |
| Diatom, *Navicula* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 17,000 | Malanchuk & Gruendling, 1973 |
| Diatom, *Navicula* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 28,000 | Malanchuk & Gruendling, 1973 |

Table 6. (Continued)

| Species | Chemical | Hardness (mg/l as $CaCO_3$) | Duration | Effect | Result* (µg/l) | Reference |
|---|---|---|---|---|---|---|
| Diatom,<br>*Navicula* sp. | Lead nitrate | - | 24 hrs | 50% reduction of $^{14}CO_2$ fixation | 17,000 | Malanchuk & Gruendling, 1973 |
| Sludge worm,<br>*Tubifex* sp. | Lead nitrate | - | 24 hrs | LC50 | 49,000 | Whitley, 1968 |
| Sludge worm,<br>*Tubifex* sp. | Lead nitrate | - | 24 hrs | LC50 | 27,500 | Whitley, 1968 |
| Snail,<br>*Goniobasis livescens* | Lead acetate | 154 | 48 hrs | LC50 | 71,000 | Cairns, et al. 1976 |
| Snail,<br>*Lymnaea emarginata* | Lead acetate | 154 | 48 hrs | LC50 | 14,000 | Cairns, et al. 1976 |
| Snail,<br>*Physa integra* | Lead nitrate | 46 | 28 days | No effect on survival | 565 | Spehar, et al. 1978 |
| Cladoceran,<br>*Daphnia magna* | Lead chloride | 45 | 21 days | LC50 | 300 | Biesinger & Christensen, 1972 |
| Cladoceran,<br>*Daphnia magna* | Lead chloride | 45 | 21 days | Reproductive impairment | 30-100 | Biesinger & Christensen, 1972 |
| Scud,<br>*Gammarus pseudolimnaeus* | Lead nitrate | 46 | 28 days | LC50 | 28 | Spehar, et al. 1978 |
| Chironomid<br>(embryo - 3rd instar),<br>*Tanytarsus dissimilis* | Lead nitrate | 47 | 10 days | LC50 | 258 | Anderson, et al. 1980 |
| Mayfly,<br>*Ephemerella grandis* | Lead nitrate | 50 | 14 days | LC50 | 3,500 | Nehring, 1976 |
| Mayfly (nymph),<br>*Ephemerella grandis* | Lead nitrate | 50 | 14 days | Bioconcentration factor = 2,366 | - | Nehring, 1976 |
| Mayfly,<br>*Ephemerella subvaria* | Lead sulfate | 44 | 7 days | LC50 | 16,000 | Warnick & Bell, 1969 |

Table 6. (Continued)

| Species | Chemical | Hardness (mg/l as $CaCO_3$) | Duration | Effect | Result* (µg/l) | Reference |
|---|---|---|---|---|---|---|
| Stonefly,<br>*Pteronarcys californica* | Lead nitrate | 50 | 14 days | Bioconcentration factor = 86 | - | Nehring, 1976 |
| Stonefly,<br>*Pteronarcys dorsata* | Lead nitrate | 46 | 28 days | No effect on survival | 565 | Spehar, et al. 1978 |
| Caddisfly,<br>*Brachycentrus* sp. | Lead nitrate | 46 | 28 days | No effect on survival | 565 | Spehar, et al. 1978 |
| Caddisfly,<br>*Hydropsyche betteni* | Lead sulfate | 44 | 7 days | LC50 | 32,000 | Warnick & Bell, 1969 |
| Rainbow trout,<br>*Salmo gairdneri* | Lead nitrate | 135 | 28 days | Inhibition of ALA-D activity | 13 | Hodson, 1976 |
| Rainbow trout (12 mos),<br>*Salmo gairdneri* | - | 135 | 14 days | Inhibition of ALA-D activity | 10 | Hodson, et al. 1977 |
| Rainbow trout,<br>*Salmo gairdneri* | Lead nitrate | 135 | 21 days | LC50 | 2,400 | Hodson, et al. 1978 |
| Rainbow trout,<br>*Salmo gairdneri* | Lead nitrate | 135 | 32 wks | Black-tails in 3 of 10 remaining fish | 120 | Hodson, et al. 1978 |
| Rainbow trout,<br>*Salmo gairdneri* | Lead nitrate | 135 | 32 wks | Increase of RBC and decreases of RBL, iron content, and ALA-D in blood | 13 | Hodson, et al. 1978 |
| Rainbow trout,<br>*Salmo gairdneri* | - | 135 | 29 wks | All fish with black tails, and decrease in ALA-D in blood | 87 | Hodson, et al. 1980 |
| Rainbow trout,<br>*Salmo gairdneri* | Lead chloride | 99 | 28 days | LC50 | 180 | Birge, et al. 1978 |
| Rainbow trout (fingerling),<br>*Salmo gairdneri* | Lead nitrate | 353 | 19 mos | Lordoscoliosis | 850 | Davies, et al. 1976 |

Table 6. (Continued)

| Species | Chemical | Hardness (mg/l as $CaCO_3$) | Duration | Effect | Result* (µg/l) | Reference |
|---|---|---|---|---|---|---|
| Rainbow trout (sac fry), *Salmo gairdneri* | Lead nitrate | 28 | 19 mos | Lordoscoliosis | 31 | Davies, et al. 1976 |
| Brook trout, *Salvelinus fontinalis* | - | - | 21 days | Stamina | 14 | Adams, 1975 |
| Brook trout (12 mos), *Salvelinus fontinalis* | Lead nitrate | 135 | 14 days | Inhibition of ALA-D activity | 90 | Hodson, et al. 1977 |
| Brook trout (embryo - 21 day), *Salvelinus fontinalis* | Lead chloride | 44 | 38 days | Elevation of ALP and ACH activity | 525 | Christensen, 1975 |
| Brook trout (12 mos), *Salvelinus fontinalis* | Lead chloride | 44 | 56 days | Decrease of hemoglobin and inhibition of GOT activity | 58 | Christensen, et al. 1977 |
| Red shiner, *Notropis lutrensis* | Lead nitrate | - | 48 hrs | LC50 | 630,000 | Wallen, et al. 1957 |
| Goldfish (<12 mos), *Carassius auratus* | Lead nitrate | 135 | 14 days | Inhibition of ALA-D activity | 470 | Hodson, et al. 1977 |
| Pumpkinseed (>12 mos), *Lepomis gibbosus* | Lead nitrate | 135 | 14 days | Inhibition of ALA-D activity | 90 | Hodson, et al. 1977 |
| Largemouth bass, *Micropterus salmoides* | Lead chloride | 99 | 8 days | LC50 | 240 | Birge, et al. 1978 |
| Fathead minnow, *Pimephales promelas* | Lead chloride | 400 | 96 hrs | LC50 | >75,000 | Tarzwell & Henderson, 1960 |
| Fathead minnow, *Pimephales promelas* | Lead acetate | 20 | 96 hrs | LC50 | 7,480 | Pickering & Henderson, 1966 |
| Mosquitofish (adult), *Gambusia affinis* | Lead nitrate | - | 96 hrs | LC50 | 240,000 | Wallen, et al. 1957 |
| Mosquitofish (adult), *Gambusia affinis* | Lead oxide | - | 96 hrs | LC50 | >56,000,000 | Wallen, et al. 1957 |
| Marbled salamander, *Ambystoma opacum* | Lead chloride | 99 | 8 days | LC50 | 1,460 | Birge, et al. 1978 |

Table 6. (Continued)

| Species | Chemical | Hardness (mg/l as $CaCO_3$) | Duration | Effect | Result* (µg/l) | Reference |
|---|---|---|---|---|---|---|
| Frog (adult), *Rana pipiens* | Lead nitrate | - | 30 days | Death | 100 | Kaplan, et al. 1967 |
| | | | SALTWATER SPECIES | | | |
| Ciliate protozoan, *Cristigera* sp. | Lead nitrate | - | 12 hrs | Reduced growth rate by 8.5% | 150 | Gray & Ventilla, 1973 |
| Ciliate protozoan, *Cristigera* sp. | Lead nitrate | - | 12 hrs | Reduced growth rate by 11.7% | 300 | Gray & Ventilla, 1973 |
| Polychaete, *Ophryotrocha labronica* | Lead nitrate | - | >600 hrs | LC50 | 1,000 | Brown & Ahsanullah, 1971 |
| Polychaete, *Ctenodrilus serratus* | Lead acetate | - | 21 days | Suppressed reproduction | 1,000 | Reish & Carr, 1978 |
| Polychaete (trochophore), *Capitella capitata* | Lead acetate | - | 96 hrs | LC50 | 1,200 | Reish, et al. 1976 |
| Polychaete, *Ophryotrocha diadema* | Lead acetate | - | 96 hrs | LC50 | 14,100 | Reish & Carr, 1978 |
| Polychaete, *Ophryotrocha diadema* | Lead acetate | - | 21 days | Suppressed reproduction | 1,000 | Reish & Carr, 1978 |
| Oyster, *Crassostrea virginica* | Field study | - | 1 yr | Bioconcentration factor = 326 | - | Kopfler & Mayer, 1973 |
| Abalone, *Haliotus rufescens* | Lead chloride | - | 6 mos | Accumulated 21 µg/g wet wt while being fed a brown alga (*Egregia laevigata*) which was pretreated with 1 mg/l | - | Steward & Schulz-Baldes, 1976 |
| Mummichog, *Fundulus heteroclitus* | Lead nitrate | - | - | 30% depressed axis formation in embryos | 100 | Weis & Weis, 1977 |

Table 6. (Continued)

| Species | Chemical | Hardness (mg/l as $CaCO_3$) | Duration | Effect | Result* (µg/l) | Reference |
|---|---|---|---|---|---|---|
| Soft shell clam, *Mya arenaria* | Lead nitrate | - | 168 hrs | LC50 | 8,800 | Eisler, 1977 |
| Mussel, *Mytilis edulis* | Lead chloride | - | 40 days | LC50 | 30,000 | Talbot, et al. 1976 |
| Mussel, *Mytilus edulis* | Lead nitrate | - | 150 days | LT50 for adults | 500 | Schulz-Baldes, 1972 |
| Mud crab, *Rhithropanopeus harisii* | Lead chloride | - | - | Delayed larval development | 50 | Benijts-Claus & Benijts, 1975 |
| Fiddler crab, *Uca pugilator* | Lead nitrate | - | 2 wks | Bioaccumulation factor = 20 | 100 | Weis, 1976 |
| Sea urchin, *Arbacia punctulata* | Lead nitrate | - | - | Few gastrula developed | 14 | Waterman, 1937 |
| Shiner perch, *Cymatogaster aggregata* | Lead nitrate | - | - | 27% inhibition of brain cholinesterase | 7.8 | Abou-Donia & Menzel, 1967 |
| Alga, *Laminaria digitata* | - | - | 30-31 days | 50-60% reduction in growth | 1,000 | Bryan, 1976 |
| Diatom, *Phaeodactylum tricornutum* | Lead chloride | - | 24 hrs | Completely inhibited photosynthesis | 10,000 | Woolery & Lewin, 1976 |
| Diatom, *Phaeodactylum tricornutum* | Lead chloride | - | 48-72 hrs | Reduced photosynthesis and respiration by 25-50% | 100 | Woolery & Lewin, 1976 |
| Diatom, *Phaeodactylum tricornutum* | - | - | 72 hrs | No growth inhibition | 1,000 | Hannan & Patouillet, 1972 |
| Diatom, *Skeletonema costatum* | Lead nitrate | - | 12 days | EC50 for growth rate | 5.1 | Rivkin, 1979 |

Table 6. (Continued)

| Species | Chemical | Hardness (mg/l as $CaCO_3$) | Duration | Effect | Result* (µg/l) | Reference |
|---|---|---|---|---|---|---|
| Diatom, *Skeletonema costatum* | Lead nitrate | - | 12 days | EC50 for maximum yield | 3.7 | Rivkin, 1979 |
| Phytoplankton, *Platymonas subcordiformis* | Lead chloride | - | 72 hrs | Retarded population growth by delaying cell division | 2,500 | Hessler, 1974 |
| Phytoplankton, *Platymonas subcordiformis* | Lead chloride | - | 72 hrs | Caused inhibition of growth and death occurred | 60,000 | Hessler, 1974 |
| Phytoplankton, *Platymonas subcordiformis* | Lead chloride | - | 2 days | 48% of cells in culture died | 2,500 | Hessler, 1974 |
| Phytoplankton, *Platymonas subcordiformis* | Lead chloride | - | 6 days | 98% of cells in culture died | 60,000 | Hessler, 1975 |
| Alga, *Dunaliella tertiolecta* | Tetramethyl lead | - | 96 hrs | EC50 | 1,650 | Marchetti, 1978 |
| Alga, *Dunaliella tertiolecta* | Tetraethyl lead | - | 96 hrs | EC50 | 150 | Marchetti, 1978 |

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* Results are expressed as lead, not as the compound.

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## Mammalian Toxicology and Human Health Effects

### INTRODUCTION

The hazards of lead exposure have been under intensive investigation for many years. Research activities continue for several reasons. First, industrial production and commercial use continues at a fairly steady rate. Second, hazardous sources persist in the environment long after the hazard-generating practice has been curtailed. A good example is the persistence of lead-base paint in houses long after the elimination of lead-containing pigments from new household paints. Finally, as biomedical science in general and toxicology in particular continue to push back the frontiers of knowledge, indices of toxicity change, generally with a consequent downward revision of what is considered an acceptable level of human exposure to environmental pollutants.

Reassessment of acceptable levels of lead exposure have been fairly numerous in recent years. These have taken the form of criteria documents and of more academically-oriented reviews. Some have been highly comprehensive, covering effects on the ecosystem in general, as well as on man [National Academy of Sciences (NAS), 1972; Boggess, 1978]. Others have been mainly concerned with effects of lead on man [World Health Organization (WHO), 1977; U.S. EPA, 1977; Hammond, 1977].

The purpose of this review is to summarize the literature which is most relevant to the question of what is an acceptable level of human exposure to lead via water. In doing so, it is necessary to consider the consequences to human health of one or another level of intake assignable to water and to the numerous other sources.

## EXPOSURE

### Natural Background Levels

Lead is ubiquitous in nature, being a natural constituent of the earth's crust. The usual concentration in rocks and in soils from natural sources ranges from 10 to 30 mg/kg. Most natural groundwaters have concentrations ranging from 1 to 10 µg/l. This is well below the United States' drinking water standard of 50 µg/l. It is much easier to specify natural levels of lead in rocks and soil than in vegetation since long-range transport of lead from man-made sources via the air inevitably contaminates both surface soil and plants growing thereon. The normal concentration of lead in rural vegetation, however, ranges from 0.1 to 1.0 mg/kg dry weight, or 2 to 20 mg/kg ash weight. Thus, nutrient movement from soil to the organic matter in plants via water does not result in any noticeable degree of biomagnification. Again, because of the impact of long-range transport of lead via air from man-generated sources, it is only possible to specify lowest concentrations found over areas of the globe most remote from human activity. These are of the order of 0.0001 to 0.001 $\mu g/m^3$, mostly measured over Greenland and over remote oceans.

Areas of abnormally high concentrations of lead occur in natural ores, usually in conjunction with high concentrations of cadmium and zinc. There is essentially no transfer from natural ore beds into overlying streams; and there is none if the soil is even slightly alkaline (Jennett, et al. 1977).

## Man-generated Sources of Lead

Lead consumption in the United States has been fairly stable from year to year at about $1.3 \times 10^6$ metric tons. Approximately half of that consumption has been for the manufacture of storage batteries and one-fifth has been for the manufacture of gasoline antiknock additives, notably tetraethyl lead and tetramethyl lead. Pigments and ceramics account for about 6 percent of annual production. All other major uses are for metallic lead products or for lead-containing alloys. The consumption of tetraethyl lead and tetramethyl lead is declining. Other uses that have significant potential for input into man are for paint pigment and solder. Paints applied to surfaces will eventually crack, flake or peel. Children are known to ingest this type of deteriorating paint. Solder also is a potential source of lead exposure either when used to seal water pipe joints or for joining seams in metal food and beverage containers.

## Ingestion from Water

Lead does not move readily through stream beds because it easily forms insoluble lead sulfate and carbonate. Moreover, it binds avidly to organic ligands of the dead and living flora and fauna of stream beds. Nonetheless, under special circumstances, lead does have considerable potential for hazardous exposure to man via drinking water. In areas where the home water supply is stored in lead-lined tanks or where it is conveyed to the water tap by lead pipes, the concentration may reach several hundred micrograms per liter or even in excess of 1,000 µg/l (Beattie, et al. 1972). There is a definite positive correlation between the concentration of lead in the domestic water supply and the concentration of lead in the blood. The concentration of lead in the water conveyed through lead pipes is dependent on a number of factors. The longer the water has stood in the pipes, the higher the lead concentration (Wong and Berrang, 1976). The lower the pH of the water and the lower the concentration of dissolved salts in the water, the greater is the solubility of lead in the water. Leaching of lead from plastic pipes has also been documented (Heusgem and De Graeve, 1973). The source of lead was probably lead stearate, which is used as a stabilizer in the manufacture of polyvinyl plastics. The magnitude of the problem of excessive lead in tap water is not adequately known. In one recent survey of 969 U.S. water systems, 1.4 percent of all tap water exceeded the 50 µg/l standard (McCabe, 1970). Special attention should be given in water quality surveillance to soft water supplies, especially those with a pH $< 6.5$. Future survey work should also indicate whether or not the water was filtered before analysis. This appears to be a common practice among water analysts. Since a substantial fraction of the lead in drinking water probably is in particulate form, filtration prior to analysis could give deceivingly low analytical values especially if a substantial fraction of the particulate lead in water is available for absorption. However, "drinking water" analyses are usually performed in unfiltered water and hence represent total lead.

## Ingestion from Food

It is generally held that food constitutes the major source of lead ingested by people. Raw fruits and vegetables acquire lead by surface deposition from rainfall, dust and soil, as well as from uptake via the root system. The relative contribution of these two sources varies greatly depending upon whether the edible portion is leafy or not. Furthermore, the nature of food processing may either lower or raise the concentration in the raw product - e.g., washing as compared to packing in metal cans with lead solder seams. There is no evidence of biomagnification in the food chain, e.g., from aquatic vegetation to the edible portions of fish and shellfish. Therefore, fish do not constitute an unusually significant source of lead in man's diet.

Schroeder, et al. (1961) reported 0 to 1.5 mg/kg of lead for condiments, 0.2 to 2.5 mg/kg for fish and seafood, 0 to 0.37 mg/kg for meat and eggs, and 0 to 1.3 mg/kg for vegetables. Other more recent studies have confirmed this observation. Many foods and beverages are packed in metal cans which have a lead-soldered side seam and caps. The concentration of lead in the contents is substantially higher after packing than before, and is also higher than the same product packed in glass [Mitchell and Aldous, 1974; U.S. Food and Drug Administration (U.S. FDA), 1975]. In some instances, the lead probably leaches from the solder through cracks or pores in the protective shellac coating applied to the inside of the can. In many other instances, however, microscopic pellets of lead splatter inside the can during the soldering process. Their availability for absorption may differ substantially from that of lead leached into solution.

Milk has been studied extensively as to lead content because it constitutes a substantial fraction of the diet of infants and young children. Whole raw cow milk has a concentration of about 9 µg/l (Hammond and Aronson, 1964) whereas market milk has an average of 40 µg/l (Mitchell and Aldous, 1974). Evaporated milk has been variously reported to contain an average of 202 µg/l (Mitchell and Aldous, 1974), 110 ± 11 µg/l (Lamm and Rosen, 1974), and 330 to 870 µg/l (Murthy and Rhea, 1971).

The daily dietary intake of lead has been estimated by numerous investigators, using either the duplicate portions approach or the composites technique wherein theoretical diets are derived using nutrition tables. The results are generally consistent, considering variations in body size and metabolic rates. Thus, Nordman (1975) reported an average daily intake of 231 µg Pb for Finnish adult males and 178 µg Pb for adult females. This is consistent with a British study reporting 274 µg Pb/day for young adults (Thompson, 1971) and with a Japanese study reporting 299 µg Pb/day for adult males doing medium work (Horiuchi, et al. 1956). The first two studies (Nordman, 1975; Thompson, 1971) described the duplicate portions technique whereas the third (Horiuchi, et al. 1956) used the composites approach. Kolbye, et al. (1974) analyzed the difficulties inherent in applying this approach. Kehoe (1961) reported an average intake of 218 µg Pb/day for sedentary men. This is not consistent, however, with two other American studies of daily fecal lead excretion (Griffin, et al. 1975; Tepper and Levin, 1972). From the lead balance studies of Kehoe (1961), it can be estimated that gastrointestinal absorption of lead approximates 8 percent. Making this adjustment, daily lead intake from the diet based on fecal lead excretion would be 113 µg in sedentary adult males (Griffin, et al. 1975) and 119 µg in women (Tepper and Levin, 1972).

Many studies of dietary lead intake are somewhat vague as to whether water consumption was included in the estimates. Others specify "food and beverages."

The dietary intake of lead in infants and young children has not been studied as extensively as it has in adults. Using the duplicate diet approach, Alexander, et al. (1973) estimated a range of 40 to 210 μg/day of lead for children ranging in age from three months to 8.5 years. Horiuchi, et al. (1956) estimated 126 μg/day of lead for youngsters 10 months old. These seemingly high values compared to adults are not too surprising considering the high caloric and fluid requirements of children in proportion to their weight.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of lead which might be ingested from the consumption of fish and shellfish. Residue data for a variety of inorganic compounds indicate that bioconcentration factors for the edible portion of most aquatic animals are similar, except that for some compounds bivalve molluscs (clams, oysters, scallops, and mussels) should be considered a separate group. An analysis (U.S. EPA, 1980) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980). The per capita consumption of bivalve molluscs is 0.8 g/day and that of all other freshwater and estuarine fish and shellfish is 5.7 g/day.

Several bioconcentration factors are available for the edible portions of bivalve molluscs:

| Species | BCF | Reference |
|---|---|---|
| Oyster,<br>*Crassostrea virginica* | 536 | Zaroogian, et al. 1979 |
| Oyster,<br>*Crassostrea virginica* | 68 | Pringle, et al. 1968 |
| Oyster,<br>*Crassostrea virginica* | 1,400 | Shuster and Pringle, 1969 |
| Auahaug, hard clam,<br>*Mercenaria mercenaria* | 17.5 | Pringle, et al. 1968 |
| Soft shell clam,<br>*Mya arenaria* | 112 | Pringle, et al. 1968 |
| Mussel,<br>*Mytilus edulis* | 650 | Schulz-Baldes, 1974 |
| Mussel,<br>*Mytilus edulis* | 200 | Talbot, et al. 1976 |
| Mussel,<br>*Mytilus edulis* | 2,570 | Schulz-Baldes, 1972 |
| Mussel,<br>*Mytilus edulis* | 2,080 | Schulz-Baldes, 1972 |
| Mussel,<br>*Mytilus edulis* | 796 | Schulz-Baldes, 1972 |

The geometric mean bioconcentration factor for lead in bivalve molluscs is 375, but no data are available for appropriate tissues in other aquatic animals. Based on the available data for copper and cadmium, the mean BCF value for other species is probably about one percent of that for bivalve molluscs. If the values of 375 and 3.8 are used with the consumption data, the weighted average BCF for lead and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 49.

### Inhalation

The third major obligatory source of lead in the general population is ambient air. A great deal of controversy has been generated regarding the contribution of air to total daily lead absorption. Unlike the situation with food and water, general ambient air lead concentrations vary greatly. In metropolitan areas average air lead concentrations of 2 $\mu g/m^3$ with excursions of 10 $\mu g/m^3$ in areas of heavy traffic or industrial point sources are not uncommon, whereas in nonurban areas, average air lead concentrations usually are of the order of 0.1 $\mu g/m^3$. In addition, people are so mobile that static air sampling devices are not very useful for estimating the integrated air lead exposure of urban populations.

### Dermal

Exposure of the skin to lead probably is significant only under special circumstances such as among workers in contact with lead-based gear compounds or greases, or blenders of alkyl lead fuel additives. It is very unlikely that the concentrations of lead in water or air are sufficient to make dermal contact a significant route of exposure.

### Miscellaneous Sources

Among adults not occupationally exposed to lead, there are several sources of lead which may assume clinically significant proportions. Perhaps the most serious widespread problem is the consumption of illicitly distilled whiskey (moonshine) which is often heavily contaminated with lead. Many cases of frank lead poisoning have been documented. The concentration of lead in moonshine whiskey commonly exceeds 10 mg/l, or 2,000 times the drinking water standard. Storage of acidic beverages in improperly glazed earthenware has caused severe, sometimes fatal poisoning in the consumer (Klein, et al. 1970; Harris and Elsea, 1967).

Occupational exposure to lead may be quite excessive. Thus, in primary lead smelters, the air lead concentration may exceed 1,000 $\mu g/m^3$. A similar situation exists in some storage battery manufacturing plants. Other hazardous occupations include welding and cutting of lead-painted metal structures, automobile radiator repair, and production of lead-base paints. In these occupations, the principal hazard is generally considered to be from inhalation of lead fumes and dusts. Hand-to-mouth transfer is probably significant.

The hazard of lead to children is of considerable concern. The number of children excessively exposed to lead from miscellaneous sources is impressive. Thus, federally assisted lead screening programs reveal that excess lead absorption was found in 11.1 percent of 277,347 children screened in 1973. Blood lead levels (PbB) were reported to be in excess of 40 µg/dl. The percentage has fallen since then, being 6.4 percent in 1974 and 6.5 percent in 1975 (Hopkins and Houk, 1976). By 1976 the problem had not changed appreciably since 1974 and 1975. In that year, 8.7 percent of 500,463 children screened had PbBs $\geq 30$ µg/dl and 2.7 percent or 13,604 children had PbBs $\geq 50$ µg/dl (Center for Disease Control, 1977).

It has long been held that the major source of elevated lead exposure in infants and young children is lead-base paint in the interior of home and in the soil surrounding the homes. More recently, the high lead content of soil and street dust attributable to the fallout of lead from automobile exhaust has become suspect. Thus, in the 1972 publication Airborne Lead in Perspective (NAS, 1972), it is pointed out that the daily ingestion of 44 mg of street dust at 2,000 μg Pb/g would suffice to elevate the PbB of a young child from 20 μg/dl to 40 μg/dl. In a survey of 77 midwestern United States cities, it was found that the average lead concentration in the street dust of residential areas was 1,636 μg/g and that in commercial and industrial areas the average concentrations were, respectively, 2,413 μg/g and 1,512 μg/g (Hunt, et al. 1971). Soil along the shoulder of heavily-traveled roadways also is heavily contaminated, although most values found have been in the range of hundreds of micrograms per gram rather than thousands (for example, Lagerwerff and Specht, 1970).

The relative contribution of soil, automotive exhaust fallout, and paint to lead exposure in children remains uncertain. There is no question that children in the age range of 1 to 5 years, in which the problem of elevated PbBs exists, do indeed exhibit pica, the habit of mouthing or ingesting nonedible objects, e.g., pieces of plastic, gravel, cigarette butts, etc. (Barltrop, 1966). The habit also appears to be more prevalent among children who have elevated PbBs than among those who do not (Mooty, et al. 1975). There is strong evidence that paint is a major source of lead in children with pica. Thus, Sachs (1974) reported that 80 percent of patients seen because of evidence of excessive lead absorption had a history of eating paint or plaster. Hammond, et al. (1977) reported that among 29 children with elevated PbBs ($\geq$40 μg/dl) selected at random from a lead screening program, all but one came from 14 homes classified as having high hazard for lead-base paint, either exterior or interior (Table 1). High hazard consisted of there being at least one accessible painted surface with $\geq$0.5 percent Pb, peeling or otherwise loose. The medium classification consisted of $\geq$0.5 percent Pb, but the painted surface was generally tight. In this study there was found to be a highly significant correlation ($p = 0.007$) between paint hazard classification (low, medium, high) and fecal lead excretion, but no correlation between fecal lead excretion and traffic density (vehicles per day) in the vicinity of the home ($p = 0.41$). Unfortunately, the correlation between traffic density and the lead content of soil and dust was not determined. Thus, the data are merely suggestive.

Ter Haar and Aronow (1974) reported that elevated lead exposure in eight children, hospitalized for excessive lead absorption, could not be caused by lead from fallout of airborne combusted automobile exhaust. Six of the eight children had distinctly elevated fecal lead excretion as compared to nine control children, yet their excretion of $^{210}$Pb, a marker for aerosol fallout, was no different from that of the controls. However, the children in this study were supposed to have ingested paint. The criteria were one or all of the following: (1) x-ray showed radio opaque materials in the gut, (2) history of pica, (3) elevated PbB, and (4) x-ray showed Pb lines on the long bones.

There is other evidence, however, which suggests that dust and soil are, under some circumstances at least, significant sources of lead for infants and children and that their effect is additive to

## TABLE 1

## Classification of Home Environments as to Lead Hazard[a]

| Family | Paint Hazard[b] | Lead Concentration, % d.w.[c] | | | Vehicles per d. x $10^3$ |
|---|---|---|---|---|---|
| | | Interior Dust | Exterior Dust | Soil | |
| A | H | - | 0.45(2) | 0.12(3) | 2.5 - 5 |
| B | H | 20 | 0.11(2) | 0.06(2) | 30 |
| C | H | - | - | 0.07(1) | 10 - 15 |
| D | H | - | 0.3(1) | 0.3(2) | 2.5 - 5 |
| F | H | 0.3(1) | 0.7(1) | 0.1(1) | =0.5 |
| G | M | - | 0.1(1) | 0.2(1) | =0.5 |
| H | H | - | 4.0(1) | 0.9(2) | 4 - 6 |
| J | H | - | 1.9(1) | - | 1 - 2 |
| L | H | - | - | 0.05(1) | 2.5 - 5 |
| M | L(I); H(E) | - | - | 0.1(3) | 0.5 - 1 |
| N | H | - | - | - | 1 - 2 |
| P | M(I); H(E) | - | - | - | 2.5 - 5 |
| R | H | - | 0.6(1) | 0 | 4 - 6 |
| S | L(I), H(E) | - | - | - | 5 - 7.5 |

[a] Source: Hammond, et al. 1977

[b] H = high; M = medium; L = low; (I) = interior; (E) = exterior. Absence of (I) or (E) designation means that both conformed to the designated classification of H, M or L.

[c] Numbers in parentheses indicate number of environmental samples.

that produced by inhalation. The best evidence is provided in a study of a population of children residing in the immediate vicinity of a large secondary lead smelter near El Paso, Texas (Landrigan, et al. 1975). Sixty-nine percent of one- to four-year-old children living within one mile of the El Paso smelter had blood lead levels greater than or equal to 40 μg/dl, the level then considered indicative of increased lead absorption. By contrast, the prevalence of blood lead levels greater than or equal to 40 μg/dl among 98 adults living in the same area was 16 percent. The geometric mean lead concentration of soil in that location was 1,791 ppm and that of house dust was 4,022 ppm. Lead based paint was not a problem. Therefore it seems likely that a proportion of the lead intake in the children living in El Paso was oral rather than by inhalation and that the net effect of the two routes of exposure was to place children at a considerably increased risk of lead uptake than adults. The mere presence of high concentrations of lead in soil accessible to children is not enough to create a hazard. Thus, children living in British homes built on soils containing 8,000 μg Pb/g showed a considerably smaller elevation of PbB than was found in the El Paso study (Barltrop, et al. 1974). This may be explained by other factors, e.g. rainfall and soil composition. El Paso, Texas is a hot, dry, windy town, whereas Britain has considerable rainfall, probably resulting in a heavy protective cover of vegetation.

Certain miscellaneous sources of lead are unique to children by virtue of the pica habit. These include colored newsprint (Joselow and Bogden, 1974) and other items to which lead-base pigment is applied. In addition, pica is known to occur in some women, particularly during pregnancy.

## PHARMACOKINETICS

In characterizing the accumulation of lead in the body under various circumstances of exposure, experimental animal data are useful for establishing relevant principles. The specific rates of transfer into, within, and outside of the animal system cannot be relied upon to reflect, with any reliability, the situation in man. Only human data will serve to indicate how much lead, in what form, and by what route the accumulation of lead in specific organs and systems would occur. This restriction has imposed severe limitations on knowledge concerning lead metabolism in man. Only certain human biological fluids and tissues are accessible for sampling, except after death. The human cadaver, in turn, has its own limitations, chiefly that the precise history of lead exposure prior to death is not known. Ante mortem studies of lead metabolism in human volunteers, on the other hand, have their own limitation. They provide a substantial amount of knowledge concerning the subject, but extrapolation of the data to the general population is tenuous. Population studies materially overcome this restriction, but at the expense of precision and detail of knowledge. By combining data from all sources, a reasonable understanding of lead metabolism does emerge, however. The ultimate objective of this section is to relate contribution of source (water) to total exposure. As will be seen, this can only be achieved by using incremental PbB as an index of water exposure - the approach also used by the U.S. EPA in assessing air as a source of lead exposure.

In reviewing the metabolism of lead in man, it is generally assumed that all inorganic forms once absorbed behave in the same manner. There is no evidence to suggest that this assumption is erroneous.

## Absorption

The classic studies of lead metabolism in man, conducted by Kehoe (1961) indicate that, on the average and with considerable day to day excursions, approximately 8 percent of the normal dietary lead (including beverages) is absorbed. This conclusion was reached as a result of long-term balance studies in volunteers. Recent studies using the nonradioactive tracer $^{204}Pb$ have confirmed this conclusion (Rabinowitz, et al. 1974). It is of special significance that these same workers found that absorption of doses of lead nitrate, lead cysteine, and lead sulfide eaten after a 6-hour fast and followed by another 6-hour fast was up to 8-fold higher than when the lead was taken with meals (Wetherill, et al. 1974). This finding has been confirmed in mice using small doses of lead (3 μg/kg) but not when using large doses (2,000 μg/kg) (Garber and Wei, 1974). Thus, lead in water and other beverages taken between meals may have a far greater impact on total lead absorption than lead taken with meals.

The gastrointestinal absorption of lead in young children is considerably greater than in adults. Alexander, et al. (1973) found that dietary lead absorption was approximately 50 percent in eight healthy children three months to 8.5 years of age. This finding has been confirmed using a larger number of subjects less than 2 years of age (Ziegler, et al. 1978). It is worth noting too that the same observation has been made using infant rats, thus suggesting a similarity in lead absorption characteristics (Forbes and Reina, 1974; Kostial, et al. 1971).

Numerous factors influence the absorption of lead from the gastrointestinal tract. Low dietary Ca and Fe and high dietary fat enhance lead absorption in experimental animals (Sobel, et al, 1938; Six and Goyer, 1970, 1972). Lead absorption has also been shown to be enhanced in experimental animals by high fat, low protein, and high protein diets, and to be decreased by high mineral diets (Barltrop and Khoo, 1975). There also has been shown to be an inverse relationship between dietary lead absorption and the calcium content of the diet of infants (Ziegler, et al. 1978). The chemical nature of the lead also has an influence on the degree of absorption. Thus, Barltrop and Meek (1975) reported that, in mature rats in an acute experiment, lead naphthenate, lead octoate, and lead sulfide were absorbed only two-thirds as well as lead acetate and that elemental lead particles, 180 to 250 μm, were absorbed only about 14 percent as well. Lead phthalate and lead carbonate were absorbed somewhat better than lead acetate. Some attention has also been given to the availability for absorption of lead in dried paint. The absorption of lead naphthenate is reduced 50 percent (in rats) as a result of incorporation in paint films (Gage and Litchfield, 1969). Similarly, it has been found in monkeys that lead octoate in dried ground paint is not absorbed to the same extent as lead octoate not incorporated into paint (Kneip, et al. 1974).

There are serious problems in regard to assessing the absorption of lead via the respiratory tract. The fractional deposition of inhaled aerosols is relatively easy to measure, even in man. The problem lies in determining the fate of the aerosol particles. To varying degrees, depending on their solubility and particle size, these particles will be absorbed from the respiratory tract into the systemic circulation, or they will be transferred to the gastrointestinal tract by swallowing following either retrograde movement up the pulmonary bed or by drainage into the pharynx from the nasal passages. Unfortunately, the particle size distribution and solubility of lead aerosols varies tremendously, depending on their origin and residence time in the air. All of these difficulties have frustrated previous attempts to assess the impact of lead inhalation on the body burden of lead. It has always proved necessary to fall back on a more indirect approach to the problem, whereby the impact of air lead concentration on the blood lead concentration is measured. In order for this approach to be meaningful, certain conditions and restrictions must apply. First, a fairly large population of subjects is needed in order to overcome the background noise resulting from the variable impact of dietary lead on the subject's PbBs. Second, it is necessary to monitor the air breathed by the subjects continuously and for a substantial period of time. Third, the subjects must have been in the air environment being evaluated for at least three months in order to assure reasonable equilibration of air lead versus PbB. If all these conditions are achieved, the results are only applicable for the particular type of lead aerosol under study. Thus, it would not be reasonable to extrapolate data obtained in a population breathing city air to a population of industrial workers for whom the greatest source of input might be lead oxide fumes. Needless to say, these restrictions are so severe that very few studies have been performed which would allow one to make a reasonable judgment concerning the relative importance of diet versus air as sources of lead absorption. An assessment of available information is deferred to the end of this section on lead metabolism.

## Dermal

Very few studies concerning the dermal absorption of lead in man or experimental animals are available. Once again, the problem of the chemical form of lead comes into play. In an early study of dermal absorption of lead in rats, it was found that tetraethyl lead was absorbed to a substantially greater degree than lead arsenate, lead oleate, or lead acetate (Laug and Kunze, 1948). Differences in the degree of absorption among the oleate, arsenate, and acetate were not significant. In a more recent study, absorption of lead acetate and lead naphthenate through the intact skin was demonstrated, based on concentrations of lead attained in various organs as compared to controls (Rastogi and Clausen, 1976). There seems to be little question that lead can be absorbed through the intact skin, at least when applied in high concentrations such as were used in the Rastogi study (0.24M).

## Distribution

The general features of lead distribution in the body are well-known, both from animal studies and from human autopsy data. Under circumstances of long-term exposure, approximately 95 percent of the total amount of lead in the body (body burden) is localized in the skeleton after attainment of maturity. By contrast, in children, only 72 percent is in bone (Barry, 1975). From animal studies it also appears that the very young retain lead to a greater extent than adults (Jugo, 1977). The amount in bone increases with old age but the amount in most soft tissues, including the blood, attains a steady state early in adulthood (Barry, 1975; Horiuchi and Takada, 1954). Special note should be made regarding the kinetics of lead distribution with reference to the blood. When human volunteers are introduced into a new air environment containing substantially higher concentration of lead than the previous one, the concentration of lead in the blood rises rapidly and attains a new apparent steady state in about 60 to 100 days (Tola, et al. 1973; Rabinowitz, et al. 1974; Griffin, et al. 1975). This is probably only an apparent steady state rather than a true one because the kinetics of disappearance of lead from the blood differ depending upon whether the high level was maintained for months or for years. When men were placed in a high lead environment for 100 days and then returned to a low lead environment, the PbB concentration returned to the pre-exposure level with a disappearance half-time of only about six weeks. By contrast, the rate of PbB decrement in workers who retire from the lead trades is much longer (Haeger-Aronsen, et al. 1974; Prerovska and Teisinger, 1970). This suggests that true equilibrium between the blood compartment and bone compartment is only slowly attained under constant state exposure conditions.

The distribution of lead at the organ and cellular levels has been studied extensively. In blood, lead is primarily localized in the erythrocytes. The ratio of the concentration of lead in the cell to lead in the plasma is approximately 16:1. Lead crosses the placenta readily. The concentration of lead in the blood of the newborn is quite similar to the maternal blood concentration. The approximate ratio of fetal to maternal PbB is somewhat greater than one (Clark, 1977; Schaller, et al. 1976). Studies of the subcellular distribution of lead indicate that distribution occurs to all organelles, suggesting that all cellular functions at least have the opportunity to interact with lead.

## Metabolism

Upon entry into the body, lead compounds occurring in the environment dissociate. Therefore, no question of metabolism of the pollutant is involved. The one exception is the family of alkyl lead compounds, principally tetramethyl lead and tetraethyl lead. These are dealkylated to form trialkyl and dialkyl metabolites, which are more toxic than the tetraalkyl forms (Bolanowska, et al. 1967).

## Excretion

The numerous studies reported in the literature concerning routes of excretion in experimental animals indicate wide interspecies differences. In most species, except the baboon, biliary excretion predominates over urinary excretion (Cohen, 1970). It also appears that urinary excretion predominates in man (Rabinowitz, et al. 1973). This conclusion, however, is based on data from one volunteer.

## Contributions of Lead from Diet versus Air to PbB

Great concern has developed in recent years regarding the impact of air lead exposure on human health in the general population. Analysis of the contribution of ambient air to lead intake by man has taken the form of an analysis of air lead versus PbB for reasons explained in the section on lead absorption. An analysis of all available data bearing on this question first appeared in the Environmental Health Criteria 3 Lead published by WHO (1977). A more rigorous and detailed analysis was published subsequently in Air Quality Criteria for Lead (U.S. EPA, 1977).

Most of the data bearing on the question of air lead versus PbB are deficient in one of two major respects. The most serious and frequent deficiency is the lack of continuous air sampling in the breathing zone of the subjects. An almost equally serious but less frequent deficiency is the lack of variation in the air lead concentration over the range of interest. This is, unfortunately, a problem seen mainly in the clinical studies (as opposed to population studies) where the number of subjects is quite limited. Another problem, also limited to the clinical studies, is the artificial nature of the lead aerosol utilized. In spite of all these apparent limitations, calculations from the epidemiologic and laboratory data sources indicate a fairly narrow range of blood Pb to air Pb ratios, namely 1 to 4 μg/dl for every microgram of air lead per cubic meter ($\mu g/m^3$). This blood Pb to air Pb ratio appears to be higher for children than adults (Table 2).

Among all the studies, the only one that satisfied all criteria for design was the one by Azar, et al. (1975). It should be

## TABLE 2

## Estimated Blood Lead to Air Lead Ratios for Four Air Lead Concentrations[a]

| Study | Population | Sample Size | Ratio at Air Lead Concentrations µg/m 1.0 | 2.0 | 3.5 | 5.0 |
|---|---|---|---|---|---|---|
| Epidemiological | | | | | | |
| Azar[b] | Adult males | 149 | 2.57 | 1.43 | 0.89 | 0.66 |
| Tepper-Levin[c] | Adult females | 1,908 | 0.87 | 0.92 | 1.00 | 1.08 |
| Nordman[c] | Adult males | 536 | | | (0.42) | |
| Nordman[c] | Adult females | 478 | | | (0.11)[a] | |
| Fugas[c] | Adults | 330 | | | (2.64) | |
| Johnson[c] | Adult males | 64 | | | (0.80) | |
| Johnson[c] | Adult females | 107 | | | (0.60) | |
| Tsuchiya[c] | Adult males | 591 | | | (3.84) | |
| Goldsmith[c] | Children males | 202 | | | (2.30) | |
| Goldsmith[c] | Children females | 203 | | | (1.70) | |
| Yankel-von Lindern[b] | Children | 879 | 1.16 | 1.21 | 1.27 | 1.37 |
| Chamberlain[d]-Williams | Adults | 482 | | | (1.10) | |
| Daines[c] | Black females | (unknown) | | | (2.30) | |
| Clinical | | | | | | |
| Griffin[c] | Adult males | 11 @ 10.9 | | | (1.40) | |
| Griffin[c] | Adult males | 14 @ 3.2 | | | (1.65) | |
| Rabinowitz[c] | Adult males | 2 | | | (1.7, 2.5) | |
| Gross[d] | Adults | (21,000 person-days) | | | (0.38) | |
| Chamberlain[d] | Adults | 7 | | | (1.20) | |
| Chamberlain[d]-Kehoe | Adults | 5 | | | (1.10) | |

[a] Source: U.S. EPA, 1977

[b] Author's regression equation evaluated at specific air lead

[c] U.S. EPA calculation

[d] Author's calculations

[e] Ratios presented in parentheses are not calculated from regression equation

noted that the regression equation developed to describe the data ($\log \text{PbB} = 1.2557 + 0.153 (\log \mu g \text{ Pb/m}^3)$) has a slope of less than one. Thus, the incremental rise in PbB for each 1 μg $\text{Pb/m}^3$ in air becomes progressively smaller. This relationship is consonant with experimental animal data showing that over a wide range of dietary lead levels the incremental rise in PbB decreases progressively proportional to the rise in dietary lead levels (Prpic-Majic, et al. 1973; Azar, et al. 1973). It also is consonant with the World Health Organization analysis of data on air lead exposure in a battery plant (WHO, 1977).

The Azar data have been analyzed as to dose response by the U.S. EPA (1977) and are presented in Table 3.

So far as the contribution of other sources of lead to PbB is concerned, a quantitive analysis such as has been done for air lead is simply not possible using the data currently available. An estimate of the total dietary contribution to PbB was attempted by WHO (1977) recently (Table 4).

So far as the specific contribution of water is concerned, information is even more scarce than for total diet. Estimates of the contribution of lead in water to PbB have been reported in four separate studies. The first of these was published in 1976 (Elwood, et al. 1976). A linear regression was calculated for PbB and water lead using "first run" morning tap water in 129 houses in northwest Wales. Blood lead concentrations were determined for an adult female resident in each house. The regression drawn was as follows:

$$\text{PbB } (\mu g/dl) = 19.6 + 7.2 \text{ (mg Pb/l water)}$$

## TABLE 3

## Estimated Percentage of Population Exceeding a Specific Blood Lead Level in Relation to Ambient Air Lead Exposure

| Air Lead, μg/m$^3$ | Percent Exceeding Blood Lead Level of: 20.0 μg/dl | 30.0 μg/dl | 40.0 μg/dl |
|---|---|---|---|
| 0.5 | 15.22 | 0.59 | 0.02 |
| 1.0 | 26.20 | 1.67 | 0.07 |
| 1.5 | 34.12 | 2.88 | 0.16 |
| 2.0 | 40.23 | 4.12 | 0.26 |
| 2.5 | 45.15 | 5.35 | 0.38 |
| 3.0 | 49.23 | 6.57 | 0.51 |
| 3.5 | 52.69 | 7.75 | 0.66 |
| 4.0 | 55.67 | 8.90 | 0.81 |
| 4.5 | 58.27 | 10.01 | 0.97 |
| 5.0 | 60.57 | 11.09 | 1.14 |
| 6.0 | 64.45 | 13.16 | 1.48 |
| 7.0 | 67.63 | 15.10 | 1.83 |
| 8.0 | 70.28 | 16.92 | 2.20 |

TABLE 4

Comparison of Daily Oral Lead Intake With PbB Levels[a]

| Study Design | Oral Intake (μg/day) | PbB[b] (μg/100 ml) | PbB per 100 μg oral Pb | Reference |
|---|---|---|---|---|
| Fecal excretion | 119[c] (women) | 15.3 | 13.0 | Tepper and Levin (1972) |
| Duplicate portion | 230 (men) | 12.3 | 5.4 | Nordman (1975) |
| Duplicate portion | 180 (women) | 7.9 | 4.4 | Nordman (1975) |
| Composites technique | 505 (men) | 34.6 | 6.8 | Zurlo and Griffini, 1973[d] |

[a] Source: WHO, 1977

[b] Contributions of air to PbB levels are not reported in most of these studies and could not be subtracted from total PbB levels.

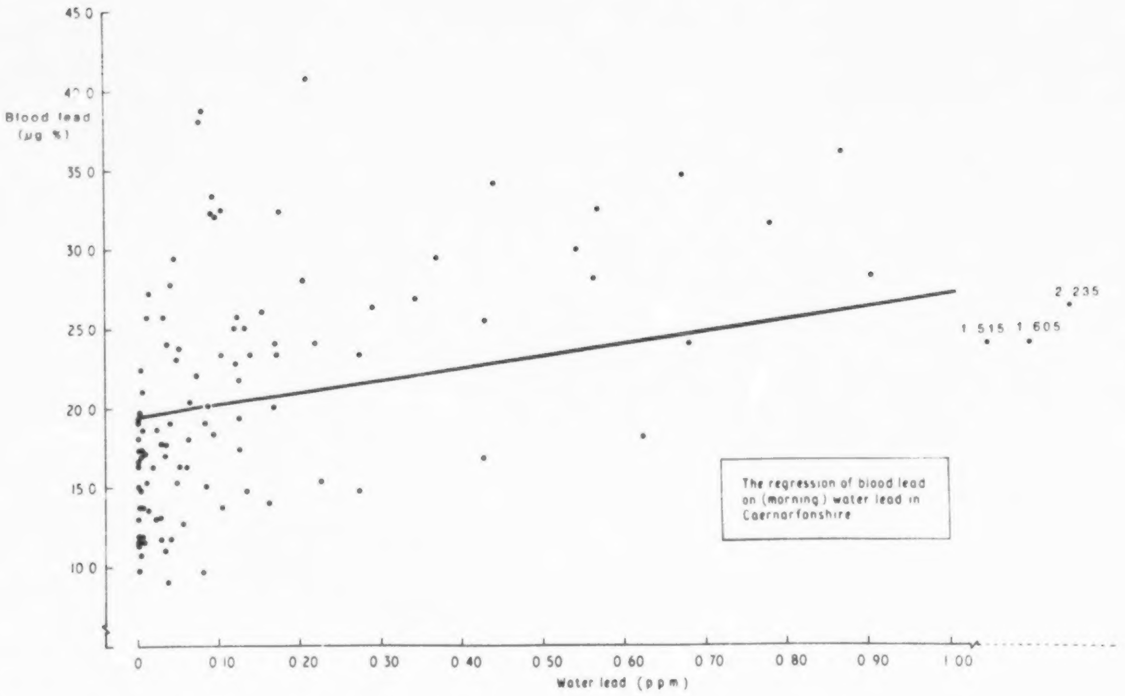
[c] Calculated from daily faecal excretion of 108 μg of lead assuming gastrointestinal absorption 10 percent

[d] Pb-B levels from Secchi, et al. 1971

The regression selection seems inappropriate from examination of the scattergram (Figure 1). A curvilinear model would have been more appropriate or at least should have been tested, particularly since the authors' linear model extrapolates to PbB 19.6 μg/dl, a rather high baseline value for non-occupationally exposed women.

Moore, et al. (1977a) reported a very similar study in which the interaction of PbB with lead in both "first flush" water and running water was determined (Moore, et al. 1977a). The study was conducted in Glasgow, Scotland, where the water is extremely soft. As in the Elwood study, blood was drawn from adult females of the household.

The Moore, et al. (1977a) study demonstrated that there is a curvilinear relationship between PbB and the concentration of lead in "first flush" water (Figure 2). The equation for the regression line was $x = 0.533 + 0.675\ y$, with both values being expressed as umol/l. Blood lead rose as the cube root of "first flush" water. Actually, there is an error in the equation. The term x really is PbB and y is the cube root of the "first flush" water. The authors point out that the lead concentration in running water probably reflects the impact of drinking water on PbB better than "first flush" water. They found that the same relationship held, wherein mean blood lead rose in proportion to the cube root of running water lead. The correlation of running water lead to PbB was even somewhat better than that of "first flush" water to PbB ($r = 0.57$ vs. 0.52). According to the authors, running water lead concentrations were approximately one-third the "first flush" lead concentrations. These data are useful in that they provide an estimate



Regression of blood-lead on morning water lead in Caernarfonshire.

FIGURE 1

Regression of Blood-lead on Morning Water Lead in Caernarfonshire

Source: Elwood, et al. 1976

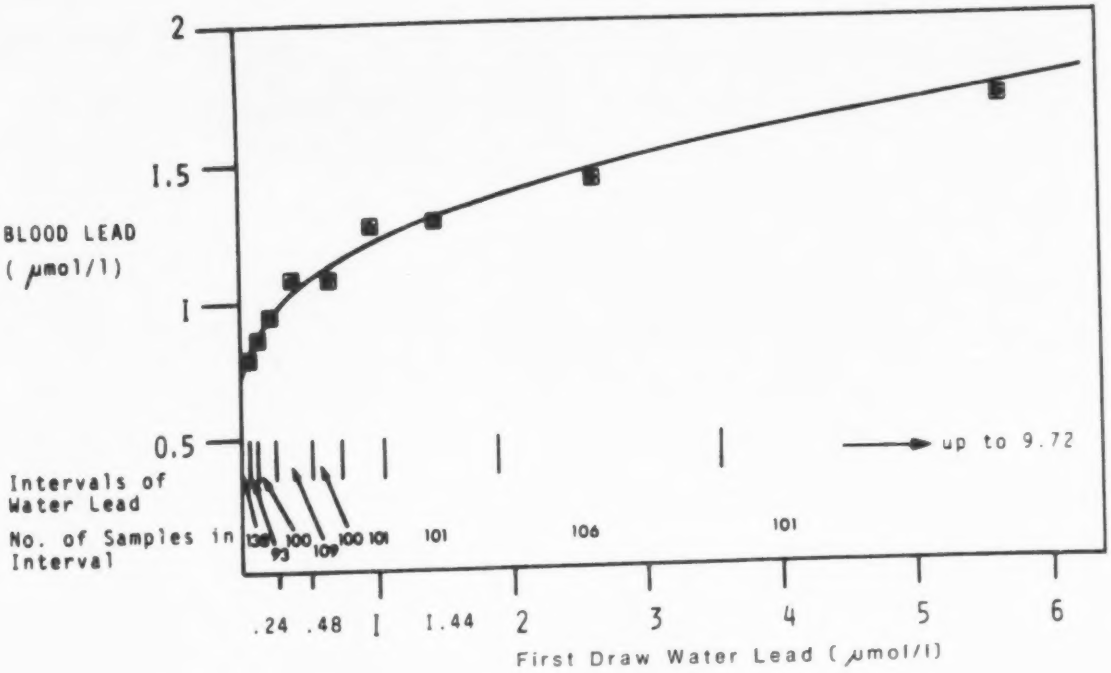


FIGURE 2

Mean Blood-lead Values for Nine Groups at Intervals of First-flush Water Lead

Source: Moore, et al. 1977a

of the consequences of changing the concentration of lead in water from one value to another. The example provided is the PbB consequence of going from a "first flush" concentration of 0.24 μmol/l (50 μg/l) to 0.48 μmol/l (100 μg/l). Such a change results in an incremental rise in PbB of 0.11 μmol/l, or of 2.3 μg/dl. On a running water basis, the PbB change would occur going from 24/3 or 8 μg/l to 48/3 or 16 μg/l. Using the authors' equation, the effect on PbB of lead in running water can be estimated (Table 5). If this relationship is correct, the impact of water lead on PbB is extremely great in the lower ranges of water lead but diminishes rapidly in the higher range of water lead (50 to 100 μg/l).

Hubermont, et al. (1978) also reports the interaction of morning tap water lead to PbB in pregnant women of the household. Again, as in the study of Moore, et al. (1977a) a curvilinear relationship is described for the interaction of PbB with water lead:

$$\text{PbB} = 9.62 + 1.74 \log \text{morning water Pb}, (\mu g/l).$$

The correlation was good ($r = + 0.37$; $p = 0.001$). The calculated impact of water Pb on PbB using this equation is considerably less in the lower range of water lead than in the Moore, et al. (1977a) study. The data may not be strictly comparable concerning water sampling procedure.

One additional set of data is available which bears on the question of the impact of the concentration of lead in water on PbB. A study was conducted by the U.S. EPA concerning the relationship of lead in drinking water to PbB (Greathouse and Craun, 1976). Both early morning and running water samples were analyzed for lead in a soft water area (Boston, Massachusetts). In addi-

## TABLE 5

## Effect of Running Water Lead on PbB*

| Pb in Levels (μmol/l) ($y^3$) | ($y^3$) Pb Levels in Running Water[a] (μg/l) | Total PbB | PbB due to Water |
|---|---|---|---|
| 0 | 0 | 11.03 | 0 |
| 0.0145 | 1 | 14.44 | 3.41 |
| 0.0725 | 5 | 16.86 | 5.83 |
| 0.1449 | 10 | 18.37 | 7.34 |
| 0.3623 | 25 | 20.99 | 9.96 |
| 0.7246 | 50 | 23.58 | 12.55 |
| 1.4493 | 100 | 26.84 | 15.81 |

[a] $y = \frac{(\mu g \text{ of Pb/l of running water})}{207} \times 3$

*Source: Moore, et al. 1977a

tion, blood samples for members of the household were analyzed for lead. These subjects included both children and adults. Numerous variables that might have influenced PbB were measured, including age, sex, traffic density, lead in dust, and socio-economic status. The data for interaction of PbB and water Pb were re-evaluated by Dr. Greathouse specifically for the purpose of comparison to the analyses of Moore, et al. (1977a) and Hubermont, et al. (1978). This was done subsequent to publication of the 1976 Greathouse and Craun report. Statistical analyses were performed using both the Hubermont model (PbB = a + b log Pb in water) and the Moore model ($PbB = a + b^3$ Pb water). These models were tested using (1) all subjects aged 20 or more, and (2) women 20 to 50. The models were also tested using running water data and early morning water data. Interestingly, the relationship of early morning water Pb to running water Pb was almost identical to the 3:1 relationship reported by Moore, et al. (1977a). More precisely, the relationship was:

$$\text{Early morning water Pb} = -0.028 + 3.081 \text{ running water Pb}$$

$$r^2 = 0.235; p = 0.0001$$

The cube root model of Moore, et al. (1977a) was more appropriate than the log water Pb model of Hubermont, et al. (1978), and the correlation of PbB with running water Pb was better than with morning water Pb. The correspondence between data from all subjects 20 years of age and over and for women age 20 to 50 was striking:

Females 20 to 50, n = 249

$$PbB = 13.38 + 2.487 \sqrt[3]{\text{running water, Pb, µg/l}}$$

$$p = 0.020$$

All subjects 20 yrs +, n = 390

$$PbB = 14.33 + 2.541 \sqrt[3]{\text{running water, Pb, } \mu g/l}$$

$$p = 0.0065$$

At this point it is useful to compare the data from the three studies discussed above. These data constitute the sole firm foundation for assessing the impact of lead in water on the internal dose of lead as reflected in PbB. The comparison is presented in Table 6. Calculations are made as to the PbB due to water over a range of 1 to 100 µg Pb/l. The comparison is made on the basis of running water Pb in spite of the fact that the equations for the two European studies were developed on the basis of "first flush" or "early morning" water. This adjustment seems justified since the ratio of these values to running water values has been affirmed to be 3:1 in two of the three studies and therefore probably is approximately correct for the third study, the one by Hubermont, et al. (1978). It is seen that the impact of lead in water on PbB is quite different among the three studies. Since there is no basis for rejecting any of the three studies, an estimate of the average situation is made from an average of the three sets of data. The reasons for any variation in the relationships can only be left to speculation. Certainly the calcium, phosphate, and iron concentrations of the waters in the three studies were different and may, to some extent at least, account for the differences in the impact of lead in water on PbB.

It is known that calcium profoundly depresses lead absorption, even over a relatively narrow range. For example, Ziegler, et al. (1978) demonstrated that a mere doubling of the dietary calcium

TABLE 6

PbB Levels due to Water Lead

| | | PbB Due to Water (μg/dl) | | |
|---|---|---|---|---|
| Running Water (μg/l) | Greathouse and Craun, 1976 | Moore, et al.[a] 1977a | Hubermont, et al.[a] 1978 | Average, All 3 Studies |
| 1 | 2.54 | 3.41 | 0.83 | 2.26 |
| 5 | 4.35 | 5.82 | 2.05 | 4.07 |
| 10 | 5.47 | 7.34 | 2.57 | 5.13 |
| 25 | 7.43 | 9.96 | 3.26 | 6.88 |
| 50 | 9.36 | 12.55 | 3.79 | 8.57 |
| 100 | 11.79 | 15.81 | 4.31 | 10.64 |

[a] These values were all calculated using morning or "first flush" water values which were taken to be three times the running water levels in the table.

level profoundly depressed lead absorption in infants. Also, animal studies have shown that nutritional iron deficiency enhances lead absorption. Attention should be given to the significance of the variations in calcium and iron content of water against the background variations of calcium and iron in nonaqueous portions of the diet. As with calcium, high phosphate levels also tend to depress lead absorption.

## EFFECTS

The effects of lead on man will be reviewed in a selective fashion. Greatest emphasis will be placed on those effects which occur at the lower levels of exposure and those which are properly viewed with the most concern, namely neurobehavioral effects, carcinogenesis, mutagenesis, and teratogenesis. Because of the paucity of data in man and the seriousness of the effect, some sections will be specifically subdivided into sections dealing with human data and animal data. In other cases, that does not seem necessary because of the wealth of human data available.

There is vast literature concerning the effects of lead on the formation of hemoglobin and more limited literature on the related effects on other hemo-proteins. From the standpoint of standard setting, the effects of lead on this system are particularly important since current knowledge suggests that the hematopoietic system is the "critical organ." That is to say that effects are detectable at lower levels of lead exposure than is the case with any other organ or system. The mechanism whereby lead reduces the circulating concentration of hemoglobin is not thoroughly understood. Many specific abnormalities exist, some occurring at lower PbBs than others. The life span of erythrocytes is shortened in heavy lead exposure (PbB = 59 to 162) (Hernberg, et al. 1967). The mechanism is not well understood, but damage to the erythrocyte membrane is likely. Dose-response and dose-effect relationships have not been established. It seems unlikely, however, that shortened cell life results in lead-induced reduction in circulating hemoglobin. Rather, it is more likely that the synthesis of hemoglobin is the critical mechanism.

Although there is evidence that lead interferes with globin synthesis as well as heme synthesis, this effect seems to occur only secondarily to a deficit in heme production (Piddington and White, 1974). Thus, it is the action of lead on heme synthesis that appears most critical. This action is complex and involves several enzymes in the synthesis of heme (Figure 3).

Clear evidence exists that lead inhibits both d-aminolevulinic acid dehydrase (ALAD) and heme synthetase both _in vitro_ and _in vivo_ at relatively low levels of lead exposure. Elevation of the concentration of the substrates for these two enzymes in plasma and urine (ALA) and in erythrocytes (PROTO) increases as PbB increases. As a matter of fact, rise in PROTO and ALA occur at PbBs somewhat below those associated with a decrement of hemoglobin. Thus, in adults, a decrement in hemoglobin first appears at PbB = 50 (Tola, et al. 1973) and at PbB = 40 in children (Betts, et al. 1973; Pueschel, et al. 1972), whereas a distinct elevation in ALA in the urine (ALAU) first appears at PbB = 40 in men (Selander and Cramer, 1970; Haeger-Aronsen, et al. 1974) and children (NAS, 1972) and somewhat lower in women (Roels, et al. 1975). Rises in PROTO first

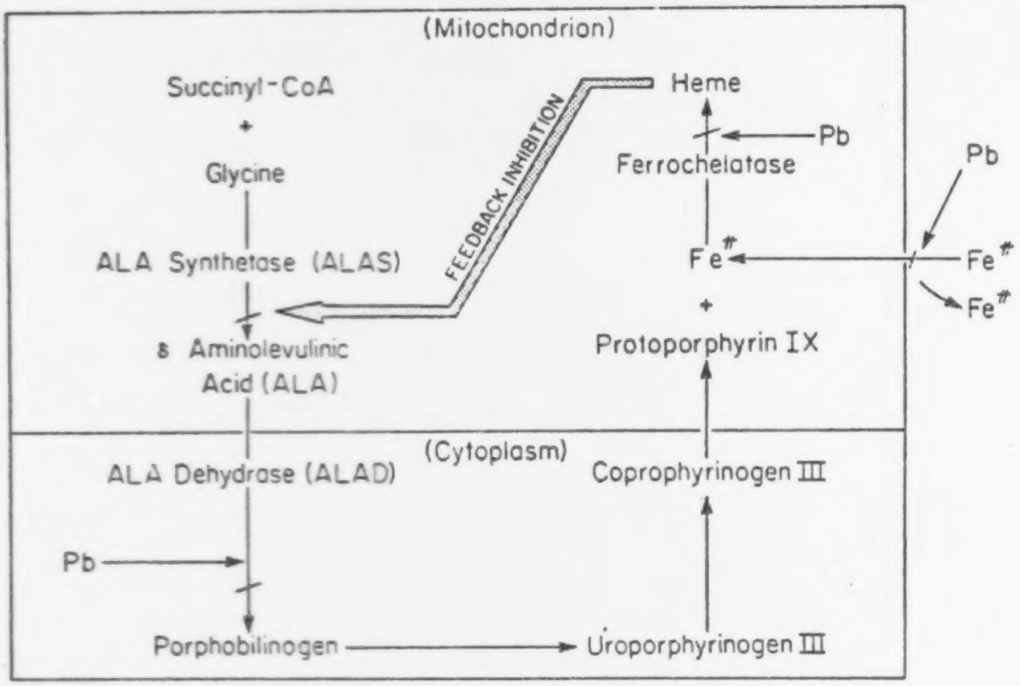


FIGURE 3

Effects of Lead on Heme Metabolism

appear at PbB = 15 to 30 in women and children and at PbB = 25 in men (Sassa, et al. 1973; Roels, et al. 1975). The most reasonable explanation for the rise in PROTO at levels of lead exposure below the threshold for hemoglobin decrement is that the primary event is inhibition of the insertion of iron into PROTO IX, whether it is caused by inhibition of heme synthetase or by inhibited entry of Fe into the mitochondrion (Jandl, et al. 1959). Regardless of that uncertainty, the effect is the same, a potential decrement in hemoglobin, which leads to feedback depression of ALAS resulting in a compensatory increase in the production of ALA and other heme precursors. The evidence for this compensatory adjustment is to be found both in laboratory animal studies (Strand, et al. 1972; Suketa, et al. 1975) and in studies of people with elevated lead exposure (Berk, et al. 1970; Meredith, et al. 1977). The approximate threshold for ALAD inhibition is PbB = 10 to 20 for adults (Tola, 1973) and PbB = 15 in children (Granick, et al. 1973). Roughly equivalent inhibition occurs concurrently in the liver of man (Secchi, et al. 1974) and in the liver and brain of rats (Millar, et al. 1970). The toxicological implications of ALAD inhibition have not been studied extensively. However, substantial lead-induced depression of blood ALAD activity in dogs does not reduce the blood-regenerating response to acute hemorrhaging in dogs (Maxfield, et. al. 1972).

A few studies have been reported concerning effects of lead on hemoproteins other than hemoglobin. Thus, the rate of cytochrome P450-mediated drug metabolism has been found to be depressed in two cases of lead poisoning (PbB = 60 and 72) but not in 10 cases where lead exposure ranged from PbB = 20 to 60 (Alvares, et al. 1975). Cytochrome content of kidney mitochondria has also been reported to be depressed in rats (Rhyne and Goyer, 1971).

The question arises as to whether certain populations may be predisposed to the toxic effects of lead as a result of G-6-PD deficiency or iron deficiency. G-6-PD deficiency is known to be associated with increased susceptibility of erythrocytes to hemolysis. The possibility of increased susceptibility of G-6-PD-deficient children to the hematopoietic toxicity of lead has not been reported. In regard to possible enhancement of hemoglobin deficiency by coexistent iron deficiency, the one study reported to date was negative. There was no significant difference in the blood hemoglobin or hematocrit among 29 iron-deficient children with PbB 20 μg/dl as compared to 17 iron-deficient children with PbB = 20 to 40 μg/dl (Angle, et al. 1975).

Dose-response relationships for the effect of lead on various parameters of hematological indices have been developed recently (Zielhuis, 1975). These are reproduced in tabular form in Table 7.

In considering these data, it is obvious that FEP (essentially PROTO) elevation is a more sensitive correlate of lead exposure than ALAU. It should also be noted, however, that an increase in FEP above normal also occurs in iron deficiency anemia. Thus, the data must be considered in that light. In a recent study of FEP in lead-exposed and non-lead-exposed children, Roels, et al. (1978) were able to study the interaction of FEP and PbB in the absence of anemia as indicated by serum iron concentration. They proposed a maximum acceptable limit for FEP at PbB = 25 μg/dl. The maximum

TABLE 7

Dose Response Relationships for the Effect of Lead on Various Parameters of Hemotological Indices[a]

| Percentage of adult female subjects with FEP levels that exceeded those found in control subjects with PbB = 20 μg/100 ml | | | Percentage of children with FEP levels that exceeded those found in control subjects with PbB= 20 μg/100 ml | | |
|---|---|---|---|---|---|
| PbB Level (μg/100 ml) | No. | % with FEP Level Higher than Normal | PbB Level (μg/100 ml) | No. | % with FEP Level Higher than Normal |
| 11-20 | 28 | 4 | 20 | 87 | 5 |
| 21-30 | 9 | 33 | 21-30 | 72 | 21 |
| 31-40 | 8 | 90 | 31-40 | 24 | 29 |
| 41-50 | | | 41-50 | 14 | |
| 51-60 | 4 | 100 | 51-60 | 12 | 64 |
| 61-70 | | | 61-70 | 10 | |
| | 49 | | | 219 | |

| Percentage of adult male subjects with FEP levels that exceeded those with PbB = 20 μg/100 ml | | | Percentage of male adults with ALA-U levels = 5 mg/l and = 10 mg/l according to PbB level | | | |
|---|---|---|---|---|---|---|
| PbB Level (μg/100 ml) | No. | % with FEP Level Higher than Normal | PbB Level (μg/100 ml) | No. | ALA-U Level (mg/l) | |
| | | | | | =5 | =10 |
| 11-20 | 26 | 0 | 11-20 | 17 | 0 | 0 |
| 21-30 | 43 | 7 | 21-30 | 27 | 0 | 0 |
| 31-40 | 32 | 19 | 31-40 | 36 | 14 | 3 |
| 41-50 | 4 | | 41-50 | 55 | 33 | 11 |
| 51-60 | 2 | 100 | 51-60 | 38 | 74 | 37 |
| 61-70 | 2 | | 61-70 | 34 | 88 | 50 |
| | 109 | | | 207 | | |

[a] Source: Zielhuis, 1975

acceptable point was the mean FEP plus two standard deviations for rural children, which equalled 79.2 μg FEP/dl erythrocytes. The PbB of these children was 9.1 μg/dl ± 0.5 with serum iron $\geq$ 50 μg/100ml. This maximum is very similar to the maximum acceptable FEP which would be calculated at mean FEP plus two standard deviations (PbB = 26 μg/dl) cited in the recent "Air Quality for Lead" (U.S. EPA, 1977). As was indicated earlier, the cooperative effect of iron deficiency and lead exposure on FEP has not as yet been adequately defined. There is just the one study by Angle, et al. (1975), suggesting no interaction at PbB = 20 to 40.

The syndrome of lead encephalopathy has been recognized since the time of Hippocrates as occurring in workers in the lead trades. The major features were dullness, irritability, ataxia, headaches, loss of memory and restlessness. These symptoms often progressed to delirium, mania, coma, convulsions, and even death. The same general effects were also described in infants and young children. Encephalopathy due to lead was probably more frequently fatal in children than in adults because lead exposure was usually not suspected and because children do not communicate signs and symptoms as readily as adults. The mortality rate among children has been variously reported as being from 5 to 40 percent.

The literature concerning the neurological features and the probable dose of lead involved is far more specific for children than for adults. This is probably because the problem persisted longer and hence benefited more from the accumulated sophistication of disease investigation. Apart from the mortality statistics, there was a considerable toll recorded among survivors in the form of long-term neurological sequelae. Cortical atrophy, convulsive seizures, and mental retardation were commonly reported (Perlstein and Attala, 1966; Byers and Lord, 1943).

The minimal level of lead exposure resulting in lead encephalopathy is not clearly known and perhaps never will be in light of the dramatic decrease in the incidence of the disease, particularly during the last 10 to 15 years. Drawing mainly from his own experiences, Chisolm (1968) has estimated the minimal PbB associated with encephalopathy as being 80 μg/dl. There are occasional reports however of occurrence of encephalopathy at PbBs below 80 μg/dl (Smith, et al. 1938; Gant, 1938). Although 80 μg/dl may be a reasonable estimate of threshold for encephalopathy in children, the usual values are much higher, with a mean of approximately 328 according to one source (NAS, 1972).

It has been reasoned that if lead exposure as specified above can have such severe deleterious effects on the central nervous system, lower levels of exposure might well result in more subtle effects. Specifically, the concern has been over whether such effects occur in children whose PbBs are in the 40 to 80 μg/dl range. Given the difficulties of study design, it is hardly surprising that all of the relevant studies are open to criticism. The most common deficiencies encountered are overlap of lead exposure in the study groups (Pb versus control), inadequate matching for socio-economic status and other variable, insensitivity of the behavioral tests, and poor knowledge of the degree of lead exposure. In regard to this last-named problem, the index of exposure has usually been PbBs determined at the time of behavioral testing.

In some instances record of one earlier PbB determination was available. In spite of these problems, when the various studies are taken together, subtle neurobehavioral effects do appear to occur as a result of exposure in the range of PbB = 40 to 80 μg/dl.

Two general approaches have been used in attacking the problem. The most common approach has been to evaluate two populations of children closely matched as to age, sex, and socio-economic status, but differing as to lead exposure. These studies are retrospective and usually strictly cross-sectional. In only one instance was a follow-up repeat study of the population performed (de la Burde and Choate, 1972, 1975). The other general approach has been to identify children with neurobehavioral deficits of unknown etiology and to establish whether their lead exposure was excessive in comparison to appropriate control children. Aside from the usual specific flaws in experimental design, there has been the additional question as to which came first, the excessive lead exposure or the neurobehavioral deficit. Among mentally subnormal children whose problems were clearly attributable to etiologies other than lead, pica incidence and PbBs were both elevated (Bicknell, et al. 1968).

Among studies of the first type, those of de la Burde and Choate (1975) are illustrative of the problems that exist in this area of toxicology. Fine motor dysfunction, impaired concept formation, and altered behavior profile were observed in 70 preschool children exhibiting pica and elevated PbBs, all of which were $>$ 30 μg/dl. The mean level was 59 μg/dl. The children were examined at four years and again at seven years of age. Both the lead-exposed group and the control group had been followed from infancy through eight years of age as part of a Collaborative Study of Cerebral Palsy, Mental Retardation, and Neurologic Disorders of Infancy and Childhood. Unfortunately, the control group did not have blood lead analyses performed. However, tooth lead and urinary coproporphyrin determinations were ultimately performed. Another problem was the inference that positive radiographic findings of lead in long bones and/or intestines were found in subjects with PbBs in the range of 30 to 40 μg/dl. Lead lines in bones at this level of exposure are extremely unlikely (Betts, et al. 1973), suggesting either that the blood lead determinations were spuriously low or that they had actually been higher at times which did not coincide with the time of sampling. Thus, it would seem that the minimal PbB associated with neurobehavioral effects may well have been more on the order of 50 to 60 μg/dl rather than 30 to 40 μg/dl. Overall, the experimental design was otherwise generally sound.

Another often-cited study by Perino and Ernhart (1974) was basically of the same general design as the one reported by de la Burde and Choate (1972, 1975). It concluded that neurobehavioral deficits occurred at PbBs as low as 40 μg/dl. The flaw in this study was that the parents in the control group were better educated than those of the lead-exposed children. Differences found may have been due to the fact that more highly educated parents train their children more on tasks related to the behavioral measures used. Low lead parent-child intelligence was correlated at 0.52 and high lead at only 0.1. The low correlation in high lead groups suggests that a factor other than parental influence was operating and probably was lead exposure.

Albert, et al. (1974) studied school-age children with a history of PbBs $\geq$60 μg/dl early in childhood. Unfortunately, PbBs for about one half of the control population were not available and some of the control children previously had PbBs $\leq$40 μg/dl.

The same types of flaws existed in studies which came up with negative results. Thus, Kotok's study (1972) had a rather wide overlap between PbBs of control subjects and lead-exposed subjects, and in another negative study fewer than half of the "lead-exposed" group had PbBs $\geq$40 μg/dl (Lansdown, et al. 1974). Another problem among negative studies has been the study of perhaps inappropriate populations. Lansdown's population consisted of British children living in the vicinity of a smelter. In another negative study, the children were Mexican-Americans also living in the vicinity of a smelter (McNeil, et al. 1975). The problem population we are dealing with in this country is of an entirely different socioeconomic character; inner city children who are predominantly socially and economically deprived. The difference in background may be significant as a determinant of behavioral ability.

In summary, there is sufficient evidence to indicate that subtle neurobehavioral effects of lead exposure occur in children exposed to lead at levels which do not result in clinical encephalopathy. The minimal level of lead exposure, the duration of exposure required, and the period of greatest sensitivity cannot be specified with any degree of certainty. However, the conclusions of two recent expert groups who have evaluated the literature in great depth are remarkably similar. The World Health Organization concluded that the probability of noticeable brain dysfunction increases in children from PbB levels of approximately 50 µg/dl (WHO, 1977), and the U.S. EPA Science Advisory Board concurred in the U.S. EPA conclusion that "the blood lead levels associated with neurobehavioral deficits in asymptomatic children appear to be in excess of 50 to 60 µg/dl." Future research may reveal that this cut-off point is actually lower. Effects of lead exposure on the peripheral nervous system of both adults and children are also documented. A number of studies have documented the occurrence of slowed nerve conduction with an approximate PbB maximum of 50 µg/dl (Hernberg, et al. 1967; Lilis, et al. 1977; Landrigan and Baker, 1976). This effect has been noted to occur at this exposure level without any overt signs of neuromuscular impairment.

Although generally considered not to be a major public health problem today, the potential damage to the brain of the fetus from lead exposure has received some attention. Beattie, et al. (1975) identified 77 retarded children and 77 normal children matched for age, sex, and geography. Of 64 matched pairs, 11 of the retarded children came from homes in which the concentration of lead in the "first flush" water exceeded 800 µg/l. By contrast, none of the control children came from such homes. In a follow-up study, PbBs from the mental retardates, taken during the second week of life, were found to be significantly higher than those of control subjects (25.5 µg/dl versus 20.9 µg/dl) (Moore, et al. 1977b). Taken at face value, those studies are extremely provocative. They suggest that the brain of the fetus is considerably more sensitive to the toxic effects of lead than the brain of the infant or young child. Lambs exposed to low levels of lead _in utero_ (PbB = 35) developed impaired visual discrimination learning behavior (Carson, et al. 1974). In spite of this seemingly low level of exposure, control animals were exposed in utero to lower levels of lead (PbB = 5) than are generally considered normal for most species. Bull and coworkers have exposed female rats to Pb from 14 days prior to breeding through weaning of pups. The normal postnatal increase in cerebral cytochromes (Bull, et al. 1978) and synaptogenesis in the cerebral cortex (McCauley, et al. 1979) were delayed by this treatment. These delays were associated with delays in the development of exploratory and locomotor behavior during the same development period (Crofton, et al. 1978). The latter effect was shown to be entirely due to exposure to Pb in utero. Blood lead concentrations on the 18th day of gestation were reported to be 31.9 µg/dl. Further work is urgently needed concerning the neurobehavioral effects of low-level lead exposure in utero.

Finally, a few comments are in order regarding neurobehavioral effects of low-level exposure in adults. A battery of performance tests were administered to 190 lead-exposed workers, along with a questionnaire (Morgan and Repko, 1974). PbBs were below 80 µg/dl in many of the workers. Unfortunately, there were many methodological problems and equipment failures which rendered the results difficult to interpret. Further, results of a similar study by other investigators were essentially negative (Milburn, et al. 1976). Thus, although it seems reasonable to suppose that neurobehavioral effects do occur at some level of exposure in workers, it is extremely difficult to specify the exposure level at which these effects may occur.

## Carcinogenicity

Three groups of investigators have reported epidemiological studies of causes of death among people overly exposed to lead. The first such study was of causes of death among 184 pensioners who died between 1926 and 1961 and of 183 men who died between 1946 and 1961 while still employed (Dingwall-Fordyce and Lane, 1963). The men were categorized as to lead exposure based on the nature of their work and, in the case of highly exposed men, on the basis of urinary lead excretion (100 to 250 µg/dl during the past 20 years and probably higher than that earlier in the work history). There is a correlation between urinary lead and blood lead, wherein 100 µg Pb/l in urine corresponds roughly to 50 µg/dl in blood (Selander and Cramer, 1970).

There were 179 men in the high exposure category for which causes of death were registered, 67 men in the category of negligible exposure and 91 men with no exposure. Although there was a significant excess number of deaths among the men who had been exposed to the greatest lead hazard, this excess could not be attributed to malignant neoplasms, as the mortality rate from this cause was actually somewhat less than expected. Furthermore, the incidence of death from malignant neoplasms in this group has actually increased in the more recent years as working conditions have improved. It seems, rather, that the excess deaths in the heavily-exposed group was due mainly to vascular lesions of the central nervous system among men employed in the lead industries during the first quarter of this century.

The second relevant study was of orchardists who at one time sprayed fruit trees with lead arsenate. A cross-sectional study of this population was conducted in 1938 by the U.S. Public Health Service (Nelson, et al. 1973). The population was classified as to exposure on the basis of whether they were adult orchard workers, (orchardists and lesser-exposed "intermediates" as separate categories), non-exposed adults of the area, and children in the area. For all categories blood lead, urine lead, and arsenic concentrations were determined. In addition, the number of years of spray exposure was recorded for the orchardists and "intermediates." There was a definite gradation in blood and urine lead concentration corresponding to the degree of exposure as classified by nature of orchard-related work or lack thereof. The orchardists had the highest PbB (x = 44 for males and 43 for females). Children of the area were intermediate (PbB = 37 in boys and 36 in girls) and adult consumers and "intermediates" had PbBs of 22 to 30.

In 1968 a follow-up study of this population was begun. Results were reported in 1973 (Nelson, et al. 1973). Of the original 1,229 study members, the status of 1,175 could be determined. Four hundred and fifty-two had died and death certificates were available for 442. No consistent differences in Standard Mortality Ratios (SMR) were observed on the basis of either exposure classification or duration of exposure. The only deviations in SMR from expected were in the direction of fewer-than-expected deaths. The mortality records for heart disease, cancer, and stroke were examined separately. Again, there was no suggestion of a relationship between lead exposure and death from any of these three major causes of death.

The most recent study of causes of death among lead-exposed workers was reported by Cooper and Gaffey (1975) and Cooper (1976). Since the results were published, the study population has been reexamined (Cooper, 1978). Results from the updated study will be discussed, although details as to lead exposure history appear mainly in the earlier publication. The objective of the study was to determine what happened to lead workers whose levels of lead absorption were below those associated with clinically-recognizable illness but above that of the general population. The population studied consisted of 2,352 smelter workers and 4,580 battery workers. Death certificates were available for 1,703 of these men. A good record of lead exposure history was considered important. Unfortunately biological monitoring programs (lead in urine or blood) were not in effect in many of the plants during the period of employment, particularly so for the deceased. Nevertheless, enough data were available to indicate that exposure was heavy. Thus, 67 percent of 1,863 workers had PbBs $\geq$40 μg/dl and 20 percent had PbBs $\geq$70 μg/dl. Twenty-six percent of the battery workers and 21.1 percent of the smelter workers had been employed for more than 20 years.

The only causes of death that showed a statistically significant elevation were "all malignant neoplasms" in the battery workers, cancers of "other sites" in battery workers and "symptoms, senility, and ill-defined conditions" in battery workers. In only one of all the cancer deaths was a renal tumor specified. Only two tumors of the brain were identified in the follow-up study. (No specification is made in the original 1975 report as to brain tumors.) The author of the 1978 report concludes that the excess deaths due to neoplasms cannot be attributed to lead "because there was no consistent association between the incidence of cancer deaths and either length of employment or estimated exposures to lead." It is not clear from reading either of the two reports concerning this population as to just how exposure categories were established.

In a letter to Science, Kang, et al. (1980) questioned the appropriateness of basing the decision of statistical significance of the results on confidence limits rather than on calcullations of a more rigorous statistical test. In their reanalysis of the results of the 1975 report by Cooper and Gaffey, Kang, et al. (1980) used the test statistic $z = \frac{\text{SMR} - 100}{100 \sqrt{1/\text{expected}}}$ and calculated a statistically significant increase in deaths due to all malignant neoplasms, cancer of the digestive organs, and cancer of the respiratory system for lead smelter workers. For battery plant workers they calculated a statistically significant increase in cancer of the digestive organs and cancer of the respiratory system. They did not calculate an increased incidence of all malignant neoplasms for these workers. Based on their calculations, the authors state "observation of a significant excess of cancer in two independent populations exposed to lead in two different industrial settings lends credibility to the suggestion that lead is an etiological factor."

In their responses to Kang, et al. (1980), Cooper (1980) and Gaffey (1980) support the methods and conclusions of their previous work.

In 1953 a study was published indicating that lead causes renal tumors in rats (Zollinger, 1953). Since that time, five other studies have confirmed this finding (Boyland, et al. 1962; Van Esch, et al. 1962; Roe, et al. 1965; Mao and Molnar, 1967; Oyasu, et al. 1970). The same observation has also been reported in mice but could not be elicited in hamsters (Van Esch and Kroes, 1969). Other studies indicate that lead also causes lung tumors in hamsters (Kobayshi and Okamoto, 1974) and cerebral gliomas in rats (Oyasu, et al. 1970). All of these studies were conducted using levels of lead exposure far in excess of tolerable human doses, but most were designed to study the mechanism of lead-induced carcinogenesis.

The first report of lead-induced renal tumors (Zollinger, 1953) was essentially a lifetime study in rats, with administration of lead beginning at 150 to 180 grams body weight and continuing for up to 9.5 months. Single weekly doses of 20 mg lead phosphate were administered subcutaneously. Of the 112 animals on lead that were examined, many died early in the study. Twenty-one had tumors. Of the 29 animals remaining after 10 months, 19 had tumors. The last animals were killed 16.5 months after initiation of the lead injections. All the tumors were renal and were classified as adenomas, cystadenomas, or papillary adenomas. Metastases were evident in only one case. According to the histological criteria for renal toxicity, all the animals receiving lead had severe lead intoxication. Among 50 control animals, none developed tumors.

The next study reported (Boyland, et al. 1962) tested the hypothesis that renal cancer due to lead was actually caused by the well-known accumulation of porphyrins associated with lead toxicity. To test the hypothesis, elevated porphyrin excretion was stimulated by administration of allyl-isopropylacetamide (AIA) in the diet of 20 rats for one year. A like number of rats were fed 1 percent lead acetate in their diet for one year. Both groups of animals were observed until they became ill or had palpable tumors. During the period of lead administration the mortality rate in the two groups was quite similar. Subsequently the lead-fed rats died earlier than the AIA rats. Subsequent to the 1-year administration of test compounds all but one of the lead-fed rats had renal tumors whereas none of the AIA group had tumors of any kind. It is not clear whether the accelerated mortality among the lead-fed rats was due to the tumors or to other toxic effects of lead.

Van Esch, et al. (1962) presented the first study in which tumor mortality was determined at more than one dosage level of lead. In this case lead was administered in the diet as basic lead acetate, 0.1 percent in one group and 1.0 percent in the other. Approximately equal numbers of males and females were used. Each lead-fed group was compared to its own set of controls, not receiving lead. Prior to the termination of the experiment, only moribund animals were killed and examined morphologically. At equivalent durations of lead administration, using these guidelines for tumor assessment, the higher dose of lead was more carcinogenic than the lower dose. Thus, at the end of 600 days of lead administration, 31 percent of the animals which survived to 400 days died from renal tumors in the 1.0 percent lead acetate group, whereas only 14 percent of the animals alive at 400 days in the 0.1 percent lead acetate group died of renal tumors (Figure 4). Mortalities with tumors in the subsequent 200-day period (600 to 800) were not comparable because in the case of the 1.0 percent lead group all the animals were killed at 730 days, whereas in the case of the 0.1 percent lead group the animals were allowed to survive until 985 days unless they became moribund. It should also be noted (Table 8) that during the first 600 days of the 0.1 percent basic lead acetate regimen, 10 of the original 26 rats (38 percent) died without renal tumors as compared to one of the original 26 in the control group (4 percent), indicating that at this level the lead regimen was lethal in some manner unrelated to its carcinogenicity. As a matter of fact, both levels of lead administration caused reduced body weight gains, suggesting toxicity unrelated to carcinogenesis.

The next study of lead-induced tumors in rats was also designed to shed light on the mechanism of lead carcinogenesis rather than to define dose-response relationships. Roe, et al. (1965) sought to establish whether testosterone or xanthopterin would influence the induction of renal neoplasms by lead in rats. In this study, the forms of lead, lead orthophosphate, and the mode of administration were unique. The lead salt was administered subcutaneously once weekly for four weeks, then intraperitoneally for nine weeks; then after a rest period of four or nine weeks, depending on the particular group of rats, lead administration was resumed for an additional 14 weeks. All the animals were males. The dosage schedule of lead is presented in Table 9, assuming an aver-

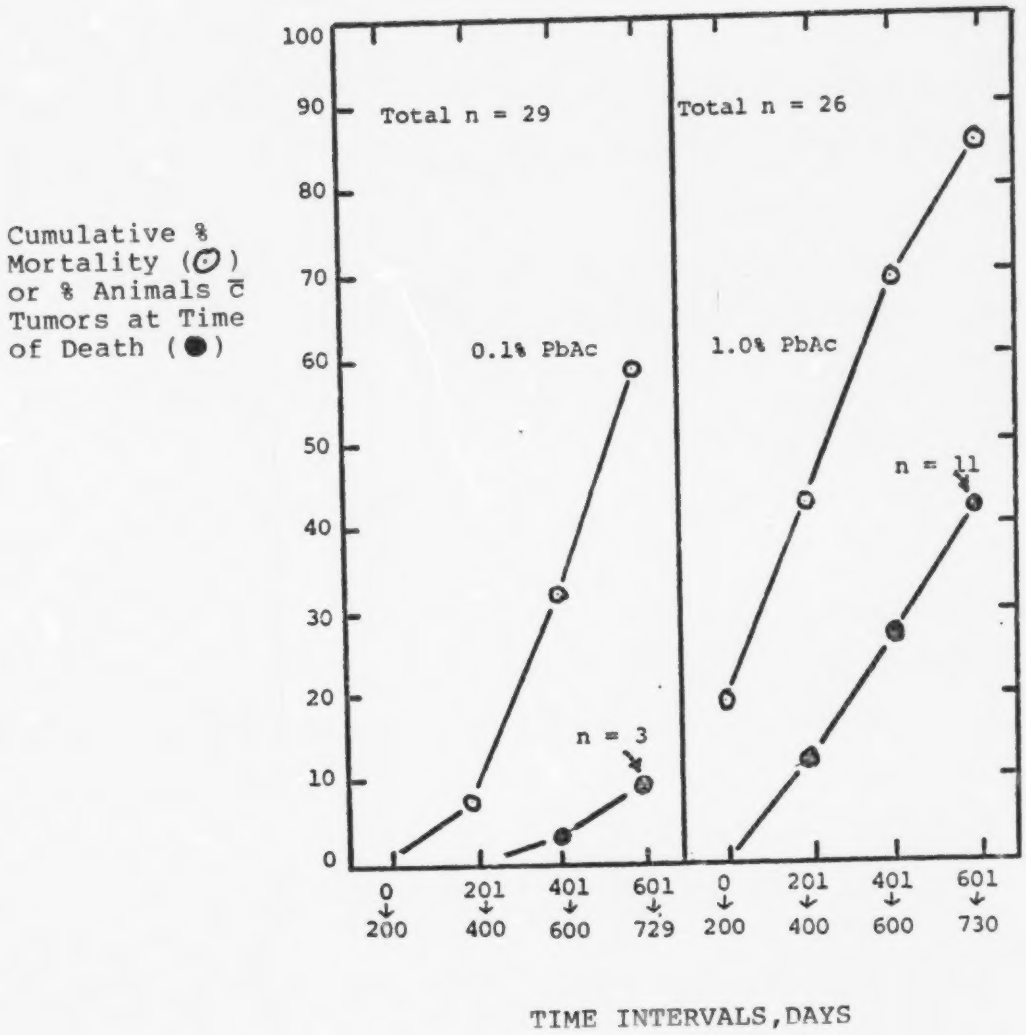


FIGURE 4

Cumulative Mortality and Tumor Incidence in Rats

Source: Van Esch, et al. 1962

## TABLE 8

Effect of Lead Exposure on the Incidence of Renal Tumors in Rats[a]

| | Successive Time Intervals, Days | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0-200 | | 201-400 | | 401-600 | | 601-729 | | 601-800 | | 800-985 | |
| | C[b] | 0.1[c] | C | 0.1 | C | 0.1 | C | 0.1 | C | 0.1 | C | 0.1 |
| n[e] at beginning of interval- | 15 | 16 | 13 | 16 | 12 | 15 | 10 | 14 | 10 | 14 | 5 | 6 |
| dead, no renal tumors | 2 | 0 | 1 | 1 | 2 | 1 | 3 | 1 | 5 | 6 | 5 | 1 |
| dead, renal tumors | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 5 |
| n at beginning of interval- | 14 | 16 | 14 | 16 | 12 | 15 | 9 | 9 | 9 | 9 | 3 | 5 |
| dead, no renal tumors | 0 | 0 | 2 | 1 | 3 | 6 | 4 | 4 | 6 | 3 | 3 | 1 |
| dead, renal tumors | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 4 |
| | C | 1.0[d] | C | 1.0 | C | 1.0 | C | 1.0 | C | 1.0 | | |
| n at beginning of interval- | 13 | 11 | 13 | 10 | 12 | 7 | 13 | 5 | 13 | 5 | | |
| dead, no renal tumors | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 12 | 1 | | |
| dead, renal tumors | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 2 | 0 | 4 | | |
| n at beginning of interval- | 13 | 13 | 13 | 9 | 13 | 6 | 13 | 2 | 13 | 2 | | |
| dead, no renal tumors | 0 | 4 | 0 | 2 | 0 | 1 | 0 | 0 | 13 | 0 | | |
| dead, renal tumors | 0 | 0 | 0 | 1 | 0 | 3 | 0 | 2 | 0 | 2 | | |

[a] Source: Van Esch, et al. 1962

[b] C = Control

[c] 0.1 = 0.1% basic lead acetate in diet

[d] 1.0 = 1% basic lead acetate in diet

[e] n = number

## TABLE 9

Dosage Schedule used by Roe, et al. (1965) in their study of the Influence of Testosterone and Xanthopterin on the Induction of Renal Neoplasms by Lead in Rats

| Group | Pb, mg/kg/d | Days on Pb | n* |
|---|---|---|---|
| Pb alone | 2.63 | 242 | 24 |
| Pb alone | 1.25 | 238 | 24 |
| Pb alone | 0.17 | 238 | 24 |
| Pb + testosterone | 1.25 | 238 | 16 |
| Pb + xanthopterin | 1.25 | 238 | 16 |
| Pb + testosterone | 0.17 | 238 | 16 |
| Pb + xanthopterin | 0.17 | 238 | 16 |
| Xanthopterin | - | 238 | 16 |
| Testosterone | - | 238 | 24 |
| No treatment | - | 238 | 24 |

*n = number

age body weight of 400 g, and averaging the dose over the total treatment period.

In analyzing the cancer data for these groups, it seems reasonable to pool all the groups receiving the same dosage of lead since neither testosterone nor xanthopterin influenced the tumor incidence. However, xanthopterin alone seemed to increase the mortality rate whereas testosterone alone did not. Therefore, only the lead alone, the lead plus testosterone, and the no treatment and testosterone alone groups are pooled here at equivalent lead dosages. The results are summarized in Table 10.

It is not possible to establish the slope of the interaction between dosage of lead and tumor incidence. The highest dose was so toxic that there were only two survivors by the time the first tumor appeared in that group (Table 10). The remaining two dosage levels, by contrast, did not cause death unrelated to tumorigenesis (Figure 5). However, since only one of these two remaining dosage levels was tumorigenic, no dose-response relationship in regard to tumorigenesis is calculable.

Interstitial nephritis occurred in all groups, including controls. Unfortunately, other manifestations of toxicity, e.g., anemia, reduced body weight gains, and food consumption were not reported. In keeping with the observations of Van Esch, et al. (1962), Boyland, et al. (1962), Mao and Molnar (1967), and Zollinger (1953), very few of the affected animals exhibited metastasis and no elevated incidence of other types of tumors was noted.

Neither of the two remaining reports concerning the carcinogenic effects of lead in rats (Mao and Molnar, 1967; Oyasu, et al.

## TABLE 10

Summary of Mortality Data Resulting from Lead Phosphate Administration to Rats[a]

Successive Time Intervals, Days

| | 0-100 | | | | 101-200 | | | | 201-300 | | | | 301-400 | | | | 401-500 | | | | 501-600 | | | | 601-700 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C[b] | 2.6[c] | 1.3[c] | .17[c] | C | 2.6 | 1.3 | .17 | C | 2.6 | 1.3 | .17 | C | 2.6 | 1.3 | .17 | C | 2.6 | 1.3 | .17 | C | 2.6 | 1.3 | .17 | C | 2.6 | 1.3 | .17 |
| n at beginning of interval | 48 | 24 | 40 | 40 | 48 | 6 | 37 | 40 | 48 | 3 | 37 | 38 | 46 | 2 | 37 | 34 | 41 | 1 | 35 | 25 | 26 | - | 14 | 18 | 11 | - | 6 | |
| dead, no renal tumors | 0 | 18 | 3 | 0 | 0 | 3 | 0 | 2 | 2 | 1 | 0 | 4 | 2 | 0 | 1 | 9 | 15 | 0 | 7 | 7 | 15 | - | 5 | 16 | 11 | 0 | 1 | |
| dead, renal tumors | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 14 | 0 | 1 | - | 3 | 0 | 0 | | 5 | |
| in interval dying with tumors | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 50 | 3 | 0 | 2 | 100 | 40 | 0 | 4 | - | 57 | 0 | 0 | - | 83 | |
| cumulative mortality, no tumors | 0 | 82 | 18 | 0 | 0 | 95 | 18 | 5 | 4 | 100 | 18 | 15 | 9 | 100 | 24 | 37.5 | 41 | 100 | 65 | 55 | 74 | 100 | 94 | 95 | 100 | 100 | 100 | 100 |
| cumulative mortality, tumors | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 3 | 0 | 2 | 4 | 35 | 0 | 4 | - | 45 | 0 | 4 | - | 58 | |

[a] Source: Roe, et al. 1965

[b] C = controls

[c] Average dose of lead phosphate, mg/kg/day

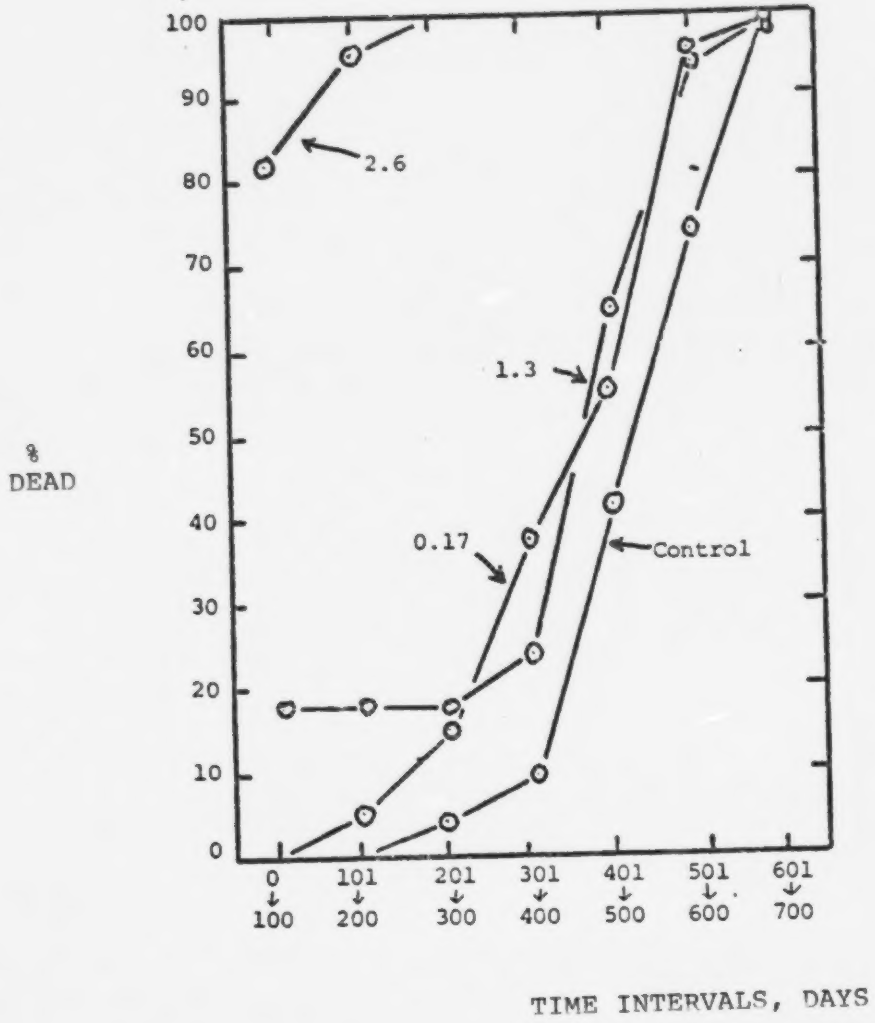


FIGURE 5

Cumulative Mortality Among Rats
not having Renal Tumors

Source: Roe, et al. 1965

1970) involved more than one level of lead administration. The results obtained by Mao and Molnar (1967) serve to confirm the results of Van Esch, et al. (1962) in that both groups used the same regimen of lead in the diet (1 percent lead acetate) and got similar incidences of renal tumors [50 percent by Van Esch (1962) vs. 77.5 percent by Mao and Molnar (1967)]. Both also noted that the first appearance of tumors was at about 300 days following initiation of lead administration. Mao and Molnar (1967) are the only authors who conducted any lead analyses. They reported 19.3 to 54.2 µg Pb/g kidney cortex as compared to 3.1 µg Pb/g in a single normal specimen. By way of comparison to man, Barry (1975) reported a mean of 0.66 µg/g in kidney cortex of 10 occupationally-exposed adult males, with a standard deviation of ± 0.56 µg/g.

Oyasu, et al. (1970) used a dietary regimen of lead subacetate for 326 to 432 days, either alone or combined with indole in one case and acetylaminofluorene (AAF) in the other. Neither of these substances alone caused renal tumors. Therefore, the data for lead with and without these additional substances could be combined. Fifty-nine percent of 130 animals receiving 1 percent lead subacetate in the diet eventually developed renal tumors. This report, incidentally, is the only one in which oral feeding of lead was to cause tumors other than renal. Eight percent of the 130 lead-fed rats developed gliomas. All but one of these were cerebral. One was cerebellar. The incidence of gliomas in animals receiving AAF alone was 2.5 percent, compared to 0.3 percent in controls. There did not seem to be any synergistic effect between AAF and lead. Lead did not cause any other types of tumors. The toxic effects of lead in this study, apart from carcinogenesis, were not reported.

Van Esch and Kroes (1969) have reported that basic lead acetate causes renal tumors in mice, but not in hamsters. These were lifetime studies with lead being incorporated into the diet beginning at five weeks of age for the mice and three to four weeks of age for the hamsters. Two levels of lead were used, 0.1 percent and 1 percent, cut back to 0.5 percent early in the study owing to toxicity. Only one renal tumor was found at the high level of lead intake in the mice, but this was probably because most of the mice died within the first 100 days of lead administration. Fourteen percent of the mice receiving 0.1 percent basic lead acetate developed renal tumors. There were no renal tumors in hamsters at either dosage level of lead. Mortality was somewhat increased at both levels of lead administration.

Another report of experimental carcinogenesis is a report of induction of lung tumors in Syrian hamsters using intratracheal injection of lead oxide (Kobayachi and Okamoto, 1974). Actually, tumors were produced only when benzo(a)pyrene (BP) was injected simultaneously with lead oxide. Neither compound alone caused tumor formation under the conditions described. This cooperative effect was obtained using 10 weekly injections. The tumors were predominantly adenomas of bronchio-alveolar origin. In addition to this effect, both lead alone and in combination with BP caused a very high incidence of alveolar metaplasia, which the authors speculate may be a preneoplastic change. BP alone caused a very low incidence of alveolar metaplasia. All treatments, including the methylcellulose injection vehicle alone caused some deaths.

The final study concerning the carcinogenic effects of lead is the most significant of all (Azar, et al. 1973). It confirms other studies showing that lead causes renal tumors in rats and that male animals are more susceptible than females. A dose-related effect is clearly evident (Table 11) (Figure 6). The dose of lead required to produce tumors did not clearly result in increased mortality among the animals; however, at dietary lead intake above 1,000 ppm, weight gains were reduced.

In summary, there is little doubt that certain compound of lead are carcinogenic or at least co-carcinogenic in some species of experimental animals.

Teratogenicity

There is little information in the literature to suggest that lead has a teratogenic effect in man. Although there were numerous reports of a high incidence of stillbirths and miscarriages among women working in the lead trades, fetal anomalies were not described. It must also be pointed out that these women were probably exposed to much higher concentrations of lead than for occupationally exposed men today. Recent literature is devoid of any references to teratogenic effects of lead in man.

In experimental animals, on the other hand, lead has been shown repeatedly to have teratogenic effects. Early studies demonstrated this in chick embryos by injection of lead into the yolk sac (Catzione and Gray, 1941; Karnofsky and Ridgway, 1952). Teratogenesis has also been observed in rodents. These studies were done using high doses of lead given intravenously or intraperitoneally. For example, McClain and Becker (1975) used single intra-

## TABLE 11

### Mortality and Kidney Tumors in Rats Fed Lead Acetate for Two Years*

| Dietary Pb[a] (ppm) | No. of Rats of Each Sex | % Mortality[b] |  | % Kidney Tumors |  |
|---|---|---|---|---|---|
|  |  | Male | Female | Male | Female |
| 5 | 100 | 37 | 34 | 0 | 0 |
| 18 | 50 | 36 | 30 | 0 | 0 |
| 62 | 50 | 36 | 28 | 0 | 0 |
| 141 | 50 | 36 | 28 | 0 | 0 |
| 548 | 50 | 52 | 36 | 10 | 0 |
| 3 | 20 | 50 | 35 | 0 | 0 |
| 1,130 | 20 | 50 | 50 | 50 | 0 |
| 2,102 | 20 | 80 | 35 | 80 | 35 |

*Source: Azar, et al. 1973

[a] Measured concentration of Pb in diet

[b] Includes rats that died or were sacrificed in extremis

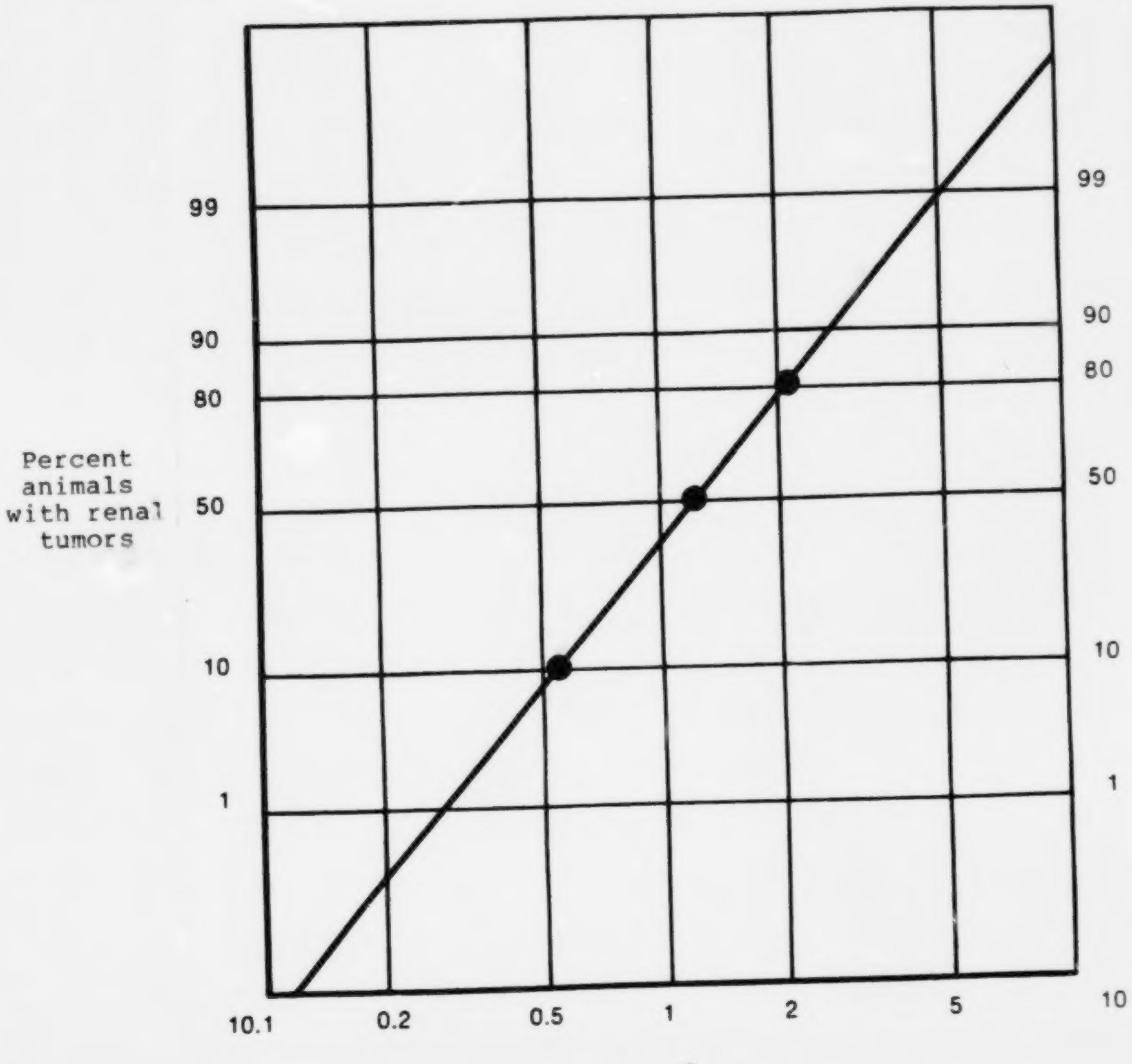


FIGURE 6

Probit Plot of Incidence of Renal Tumors in Male Rats

Source: Azar, et al. 1973

peritoneal doses of 25 to 70 mg/kg in rats. They found that teratologic effects occurred when administration was on day 9. Administration later in pregnancy resulted in embryotoxicity (fetal resorption) but not in teratogenic effects. Carpenter and Ferm (1977) observed teratologic effects in hamsters following the administration of 50 mg/kg $Pb(NO_3)_2$ intravenously on day 8. Chronic administration of lead in the drinking water of pregnant rats at very high concentrations (up to 250 mg/l) resulted in delayed fetal development and fetal resorption without teratologic effects (Kimmel, et al. 1976).

In summary, it seems that, in man, embryotoxicity precedes teratogenicity in the lead sensitivity scale. This is supported by historical experience in occupationally exposed women and by animal studies.

## Mutagenicity

Pertinent data could not be located in the available literature concerning the mutagenicity of lead.

## Reproductive Effects

As was indicated in the previous section, lead has been known to cause miscarriages and stillbirths in women working in the lead trades during the latter half of the 19th century and probably on into the early part of the 20th century. It is very difficult to estimate minimally toxic exposure for stillbirth and miscarriages because exposure data, e.g., PbB are lacking for women who experienced this problem. The minimally toxic level of exposure may actually be quite low. Lane (1949) reported on the outcome of 15 pregnancies incurred among 150 women working in an unspecified lead trade during World War II. Three of these women had miscarriages - an incidence seven times normal. Unfortunately the numbers were too small to be assigned statistical significance. Lead exposure was modest, air lead being 75 $\mu g/m^3$ and urinary lead excretion in men working with these women being 75 to 125 µg/l. A more recent Japanese study also is suggestive of miscarriages occurring among women with only modest exposure (Nogaki, 1958). These women were the wives of lead workers. Unfortunately, the actual level of lead exposure was not reported.

It has recently been reported that the incidence of premature fetal membrane rupture in term and preterm infants is much higher 30 to 50 miles west of a lead mining area of Missouri (17 percent) than in a Missouri urban area remote from lead mining activities (0.41 percent) (Fahim, et al. 1976). Maternal and fetal PbBs at birth also differed significantly for normal births vs. births with premature membrane rupture. Maternal and fetal PbBs for the normal deliveries were about 14 and 4 µg/dl, respectively, whereas they were about 26 and 13 respectively for mothers and infants with membrane rupture. This provocative study needs confirmation. It is difficult to understand, for example, why fetal PbB should be so much lower than maternal PbB in all groups.

There is a possibility that lead affects fertility as well as the conception. Lancranjan, et al. (1975) reported that significant levels of teratospermia occurred among men working in a lead storage battery factory. Their PbBs were 30 to 80 µg/dl. Although many studies have attempted to correlate semen quality with fertility, the extent to which abnormally-shaped sperms participate in fertilization is unclear. Experimental animal studies have shown reduced fertility of both maternal and paternal origin (Stowe and Goyer, 1971).

There have been numerous conflicting reports concerning the occurrence of chromosomal aberrations in lymphocytes of lead-exposed workers (O'Riordan and Evans, 1974; Forni, et al. 1976). The reason for these conflicting findings is not clear. DeKnudt, et al. (1977a) suggest that ancillary factors may be critical; for example, the level of calcium intake. They base this conclusion on the lack of correspondence between lead effects in two widely separated lead-using plants, one being a secondary lead smelter and the other being a plant manufacturing "tin" dishes. Lead exposures were roughly comparable: PbBs were on the order of 45-100 µg/dl. Severe chromosomal aberrations were found in one plant whereas no such effects were seen in the other. They further point out that no severe aberrations have been seen in at least some animal studies in which lead exposure was heavy and nutrition apparently adequate (Jacquet, et al. 1977; De Knudt, et al. 1977b). The implications of chromosomal aberrations which have been reported are not known. A recent report by Wibberley, et al. (1977), which demonstrates a striking increased incidence of high placental lead associated with stillbirths or congenital malformations, further suggests that a relationship exists between intrauterine exposure to lead and reproductive casualty.

## Renal Effects

There is considerable information in man concerning the renal effects of lead. Two distinctive effects occur in both adults and children. One is reversible proximal tubular damage, which is seen mainly with short-term exposure. The other effect is reduced glomerular function which has generally been considered to be of a slow, progressive nature.

Tubular damage is manifested as the Fanconi triad of glycosuria, hypophosphatemia with phosphaturia, and generalized aminoaciduria. The last-named manifestation appears to occur more consistently than either glycosuria or phosphaturia. It was first described more than 20 years ago in lead smelter workers (Clarkson and Kench, 1956). In adults, the condition probably is uncommon at PbBs below 70 µg/dl. Thus, in a recent series of seven workers, all of whom had PbBs 70 µg/dl, with a range of 71-109, none had aminoaciduria or glycosuria. Significantly, five had hemoglobins below 12 g/dl (Cramer, et al. 1974). Similarly, in a series of 15 infants hospitalized for lead poisoning, all having PbBs $\geq$100 µg/dl at entry, only three had aminoaciduria, with PbBs of 246, 299, and 798 µg/dl (Chisolm, 1968).

Reduced glomerular filtration with attendant rise in serus urea concentration is generally considered to be a progressive disease, implying prolonged lead exposure. It is accompanied by interstitial fibrosis, obliteration of glomeruli and vascular lesions (Morgan, et al. 1966). It occurs at relatively low levels of lead exposure, at least relative to the levels associated with aminoaciduria. For example, in Cramer's series of seven workers, none of whom had aminoaciduria, three had low renal clearance of inulin ($<$90 ml/min/$1.73m^2$). In another study of eight men with occupational lead exposure (PbBs = 29-98), four had reduced glomerular filtration rates (Wedeen, et al. 1975). Of these four cases, one had a PbB of 48 μg/dl at entry. The maximal PAH secretion rate ($Tm_{PAH}$) was also reduced, indicating coexistent tubular damage. Among the other three cases, two had only a marginal depression of $Tm_{PAH}$.

From these and other studies, it appears that the kidney is sensitive to glomerular-vascular damage, with an imprecisely known threshold for effect which may be below PbB = 50 ug/dl.

## Cardiovascular Effects

Dingwall-Fordyce and Lane (1963) reported an excess mortality rate due to cerebrovascular disease among lead workers. These workers were employed during the first quarter of the 20th century when lead exposure was considerably higher than it has been more recently. There was no similar elevated mortality among men employed more recently however. Similarly, in Cooper's more recent epidemiological study there was no excess mortality attributable to stroke or other diseases associated with hypertension or vasculopathy (Cooper and Gaffey, 1975; Cooper, 1978). It would appear from these studies that the vascular effects of lead only occur with heavy industrial lead exposure - probably in excess of what is encountered today.

There have been reports of heart failure (Kline, 1960) and of electrocardiographic abnormalities (Kosmider and Pentelenz, 1962) attributable to lead exposure. However, these cases have always involved clinical lead intoxication. It does not seem likely, therefore, that the heart is a critical target for lead effects.

## Miscellaneous Effects

Sporadic reports of other biological effects of lead in man exist, but these are difficult to evaluate as to associated lead exposure. They have frequently been reported only at high exposure levels and only by one or two investigators. For example, Dodic, et al. (1971) reported signs of impaired liver function in 11 of 91 patients hospitalized for lead poisoning. No information was provided as to indices of lead exposure. Impairment of thyroid function has been reported in moonshine whiskey drinkers hospitalized for lead poisoning (Sandstead, et al. 1969). The degree of lead exposure was not clearly indicated, but it can be assumed to have been high. Intestinal colic has long been recognized as a sign of lead in industrially exposed people. It probably also occurs in children with lead poisoning. Beritic (1971) reported that it occurs with PbBs as low as about 40 µg/dl. This seems unlikely since the cases he reported also were anemic, a condition associated with the considerably higher PbBs. A number of studies have suggested that a relationship exists between lead exposure and amyotrophic lateral sclerosis (ALS). The most recent report on this examined plasma lead levels in 16 cases of ALS and in 18 controls and found significant differences at the 0.05 level (Conradi, et al. 1978).

Finally, animal studies indicate that relatively high levels of lead exposure interfere with resistance to infectious disease (Hemphill, et al. 1971; Gainer, 1974). There are no reports of an abnormal infectious disease incidence among people with high lead exposure, however.

## CRITERION FORMULATION

### Existing Guidelines and Standards

Since lead is ubiquitous in the environment, several government agencies have become involved in regulating its use. The most recent action was taken by the Consumer Product Safety Commission (CPSC). In 1977 the CPSC lowered the maximum allowable concentration of lead in house paint to 0.06 percent. At present the Occupational Safety and Health Administration (OSHA) is preparing a set of regulations regarding occupational lead exposure. Similarly, the U.S. EPA has set an ambient air lead standard. The U.S. FDA has provided new guidelines for the regulation of sources of lead in foods and cosmetics. Given the multi-media nature of lead exposure to man, it is essential that any action taken in regard to one source, such as water, be coordinated with similar actions being taken for other media such as air and diet.

### Current Levels of Exposure

Approximately 1 percent of tapwater samples have been found to exceed the current standard of 50 µg/l. This is generally a problem in softwater areas, particularly where lead pipes convey the water supply to the tap from the surface connection. The contribution of the diet is approximately 200 µg/day for adults. For children (ages three months to nine years) the diet contributes 40 to 200 µg of lead per day. On the basis of current information, it is impossible to judge how much dietary lead is attributable to the water used in food preparation. The concentration of lead in ambient air ranges from approximately 0.1 $\mu g/m^3$ in rural areas to as much as 10 $\mu g/m^3$ in areas of heavy automotive traffic.

## Special Groups at Risk

In addition to these usual levels of exposure from environmental media, there exist miscellaneous sources which are hazardous. The level of exposure resulting from contact is highly variable. Children with pica for paint chips or for soil may experience elevation in blood lead ranging from marginal to sufficiently great to cause clinical illness. Certain adults may also be exposed to hazardous concentrations of lead in the workplace, notably in lead smelters and storage battery manufacturing plants. Again, the range of exposure is highly variable. Women in the workplace are more likely to experience adverse effects from lead exposure than men due to the fact that their hematopoietic system is more lead-sensitive.

## Basis and Derivation of Criterion

The approach that will be taken here in assessing the impact of lead in water on human health is basically the same as has been taken by the U.S. EPA (1977) for lead in air. The critical target organ or system must first be identified. Then, the highest internal dose of lead that can be tolerated without injury to the target organ must be specified. Finally, the impact of lead in water on the maximum tolerated internal dose must be estimated, as well as the likely consequences of specific reductions in the maximum allowable concentrations of lead in water.

In identifying the critical organ or system, great reliance is placed on the concentration of lead in the blood (PbB) as an index of internal dose. Such an indirect measurement is necessary because of the multi-media character of lead intake. It is virtually impossible to measure total lead intake in people in any meaningful way. Because intake and output fluctuate greatly from day to day, measurement of total lead intake would require long-term balance studies. Variables have a substantial influence on the rate and degree of lead uptake from the external environment. Some groups have proposed alternatives to PbB as a measure of internal dose, e.g., FEP and tooth lead. FEP is not suitable because it is a biological response to lead. As such, it is subject to influences other than lead, notably iron deficiency. Tooth lead is a potentially useful index of lead exposure, but with the present state of the art being what it is, tooth lead is difficult to interpret. It only provides an integrated profile of past lead exposure. One is not able to say when the exposure occurred. It has the additional limitation of not being available on demand. Teeth are shed spontaneously only in childhood. Moreover, only a very small data base is available for dose-effect and dose-response using any measure of dose other than PbB. The use of PbB as a measure of internal dose is widely accepted, simply because nothing better is available.

Having specified that PbB is the best measure of internal dose currently available, the next question concerns the lowest PbB levels at which adverse health effects occur. Two recent documents (U.S. EPA, 1977; WHO, 1977) have been published in which judgments were rendered in this regard (Table 12). It will be noted that the estimates are strikingly similar. The estimated no-effect levels are based on limited populations and probably are lower to some undefinable degree in the total population at risk. Slightly more information was available to the U.S. EPA panel than to the WHO

## TABLE 12

### Summary of Lowest PbBs Associated with Observed Biological Effects in Various Population Groups[a]

| Lowest Observed Effect Level (μg Pb/100 ml Blood) | Effect | Population Group |
|---|---|---|
| 10 | ALAD inhibition | Children and adults |
| 15-20 | Erythrocyte protoporphyrin elevation | Women and children |
| 25-30 | Erythrocyte protoporphyrin elevation | Adult males |
| 40 | Increased urinary ALA excretion | Children and adults |
| 40 | Anemia | Children |
| 40 | Coproporphyrin elevation | Adults and children |
| 50 | Anemia | Adults |
| 50-60 | Cognitive (CNS) deficits | Children |
| 50-60 | Peripheral neuropathies | Adults and children |
| 80-100 | Encephalopathic symptoms | Children |
| 100-120 | Encephalopathic symptoms | Adults |

No Observed Effect Levels in Terms of PbB[b]

| No Observed Effect Level (μg Pb/100 ml Blood) | Effect | Population Group |
|---|---|---|
| 10 | Erythrocyte ALAD inhibition | Adults and children |
| 20-25 | FEP | Children |
| 20-30 | FEP | Adult females |
| 25-35 | FEP | Adult males |
| 30-40 | Erythrocyte ATPase inhibition | General |
| 40 | ALA excretion in urine | Adults and children |
| 40 | CP excretion in urine | Adults |
| 40 | Anaemia | Children |
| 40-50 | Peripheral neuropathy | Adults |
| 50 | Anaemia | Adults |
| 50-60 | Minimal brain dysfunction | Children |
| 60-70 | Minimal brain dysfunction | Adults |
| 60-70 | Encephalopathy | Children |
| 80 | Encephalopathy | Adults |

[a] Source: U.S. EPA, 1977

[b] Source: World Health Organization, 1977

panel since it reviewed literature through mid-1977, whereas the WHO expert groups reviewed literature only through 1976. In addition, the U.S. EPA performed statistical calculations based on the known distribution of blood lead levels in the United States.

Both sets of data in Table 12 are in error in one regard. They use the term "anemia" inappropriately under the "Effect" column. What they really mean is "decrement in hemoglobin." Anemia is a clinical term used to denote a degree of hemoglobin decrement which is below the normal range for that class of individuals, e.g., men or children.

The question that arises in considering Table 12 is which is the critical effect? Precisely the same issue confronted the U.S. EPA in its deliberations concerning establishment of a national ambient air quality standard for lead (42 FR 630979). It focused on the lead effects in children since they are more sensitive than adults.

It ruled that the maximum safe blood lead level for any given child should be somewhat lower than the threshold for a decline in hemoglobin level (40 µg Pb/dl). In considering how much lower this limit should be, the U.S. EPA cited the opinion of the Center for Disease Control, as endorsed by the American Academy of Pediatrics, that the maximum safe blood lead level for any given child should be 30 µg/dl. Based upon epidemiological and statistical considerations, the U.S. EPA estimated that if the geometric mean PbB were kept at 15 µg/dl, 99.5 percent of children would have PbB $\leq$30 µg/dl. This position provides a substantial margin of safety which accomodates minor excursions in lead exposure due to adventitious sources. Controls on lead in obligatory media (e.g., air and water) do not protect children from the hazards of pica for lead-base paint chips or soil and dust contaminated with lead from such sources as fallout from the smoke zone of lead smelters.

In its deliberations concerning an ambient air lead standard, the U.S. EPA estimated that the contribution of sources other than air to PbB is 10 to 12 µg/dl. This is presumably composed overwhelmingly of dietary sources which, in turn, is composed of both food and water.

The next question concerns the contribution of water to lead exposure. Only three useful studies of the interrelationship between PbB and lead in drinking water are available. Overall, the Moore, et al. (1977a) study, the one by Hubermont, et al. (1978), and the calculations made from U.S. EPA data collected in the Boston area (Greathouse and Craun, 1976) are credible because they are consistent with other information concerning the curvilinear relationship between PbB and air Pb. The implication of the equation describing the relationship between PbB and water lead is that with increasing lead in water, the incremental rise in PbB becomes progressively smaller, as with air lead vs. PbB and dietary lead vs. PbB (see "Contributions of Lead from Diet vs. Air to PbB" in the Pharmacokinetics section). The water lead vs. PbB relationship differs in one significant respect, however, from the air lead vs. PbB relationship in that the baseline PbB (0 water PbB) is independent of the contribution of water lead to PbB. Thus, regardless of whether one starts with a baseline PbB of 11 µg/dl, as was indicated in the Moore, et al. (1977a) study or whether one starts at some other PbB level, e.g., 20 μg/dl, the add-on PbB from any given level in water will be the same. Such is not the case in the Azar analysis of air Pb vs. PbB (see "Contributions of Lead from Diet vs. Air to PbB" in the Pharmacokinetics section). Here, the higher the baseline, the less is the contribution of air Pb. This is because log PbB is proportional to baseline PbB + log air concentration. Future research may provide better insight into whether this discrepancy is real and, if so, why. The question is of some practical importance. For instance, if you have a baseline PbB (no lead in water) of 30 μg/dl, such as in a child acquiring lead from paint, it would be of some importance to know whether an additional increment of lead in water would have the same impact on PbB as it would in a child having a baseline of PbB of 10 μg/dl. An Azar-type model would suggest a lesser impact starting from the higher baseline PbB.

So far as a specific recommendation regarding a water quality for Pb is concerned, a stand must be taken using the available data. Beginning with the assumption that a PbB of 12 μg/dl is essentially attributable to food and water and that the average lead content of water consumed is 10 μg/l, approximately 5 μg Pb/dl blood (from Table 6) is attributable to the water that is used in food and beverage preparation and in direct consumption. If the water Pb were consistently consumed at the present Pb standard of 50 μg/l instead of at 10 μg/l, an additional contribution of approximately 3.4 μg/dl to PbB would result (8.57 - 5.13 from Table 6). This would yield a total PbB of 12 + 3.5 or 15.4 μg/dl, the approximate maximum geometric mean PbB compatible with keeping 99.5

percent of the population under PbB = 30 µg/dl. Thus, based on most recent data, the present water standard of 50 µg Pb/l may be viewed as representing the upper limit of acceptability. This criteria is based on empirical observation of blood lead in human population groups consuming their normal amount of water and food daily. Specific amounts of foods or drinking water consumed were not quantified, but it can be assumed that they reflect an average consumption of water, fish, shellfish, and other foods.

All the assumptions that have been made in arriving at an estimate of the impact of lead in water on PbB have been on the conservative side. For instance, unpublished data from the Commission of the European Communities suggest that the impact of lead in water on PbB is appreciably less than has been estimated from published data used in this document [personal communication from Alexander Berlin, et al. (1978), Commission of the European Communities, Luxembourg][1]. Furthermore, data from a study (Morse, et al. 1978) of the effect of lead in water on the PbB of a population of children in a relatively small town are reassuring. They indicate that among children whose water supply contained 50 to 180 µg Pb/l, PbBs averaged 17.2 µg/dl[2].

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[1] Subsequent to the writing of this report, these data were submitted to the EPA by Dr. Berlin. They were studied and judged not to alter the conclusions arrived at in this document concerning PbB vs. lead in water (see Appendix).

[2] It should be pointed out, however, that the contribution from other sources is not indicated, thus, the relative water lead contribution is unknown.

Finally, there remains the issue of the carcinogenic effects of lead. Using data from one species of laboratory animal (the rat) it was possible to construct a seemingly valid dose-response curve and to calculate a dietary level of lead which would predict an incidence of cancer in 1:100,000 people. This calculated dietary level of lead is 29 μg/kg. Since this estimate includes lead from all sources, its implications are beyond the scope of this document. It should be noted, however that the International Agency for Research on Cancer, Lyon, France considers the experimental animal evidence to be of dubious significance with regard to man (IARC, 1972).

The Agency has not yet resolve all of the issues concerning the potential carcinogenicity of lead, but will complete its review in the near future. All of the data will be subjected to an extensive peer review by outside experts and in-house scientists. Depending upon the final conclusions of the review, the water quality criteria for lead may be re-evaluated.

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# APPENDIX*

Results of the research examined in the Commission of the European Communities (CEC) paper are summarized in Tables 1 and 2. The data presented in Table 1 are equations developed by the authors concerning the relationship of blood lead (PbB) to water lead (PbW). Table 2 consists of calculations of the contribution of 100 µg Pb/l of water to PbB (as µg/dl). Some of these calculations were made by Berlin, et al. (1978), interpolating from data points in the articles cited. Others were made using the equations provided by the authors of the articles cited.

Three types of equations are presented:

(1) $\text{PbB} = a + b\ \text{PbW}$

(2) $\text{PbB} = a + \log \text{PbW}$

(3) $\text{PbB} = a + \sqrt[3]{\text{PbW}}$

In all cases "a" is the baseline expressing PbB at PbW = 0. Of these three mathematical relationships, the third appears to be the most valid for two reasons: (1) the largest number of subjects are involved in studies using this equation, and (2) it corresponds to the analysis of U.S. EPA data (Greathouse and Craun, 1976) as cited in the lead criterion document, which also involved a very large number of subjects. Moreover calculations made of PbB vs. PbW using the U.S. EPA data were for females aged 20 to 50, a sub-population which probably gets a larger proportion of its water from

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*Summary of "Research of PbB vs. Lead in Drinking Water in Europe" as presented by A. Berlin, et al. (1978), Commission of the European Communities.

## TABLE 1

## Relationships between PbW and PbB*

| Relationship | Remarks | Reference |
|---|---|---|
| $PbB = 0.018\ PbW + 22.9$ | $r = 0.417$<br>$PbW = \mu g/1$<br>$PbB = \mu g/100\ ml$<br>First morning flush | Addis and Moore, 1974 |
| $PbB = 0.76 + 0.15\ PbW$ | PbW and PbB in μmol/1<br>$r = 0.58$, first morning flush | Moore, 1977a |
| $PbB = 0.80 + 0.20\ PbW$ | $r = 0.52$, running sample | |
| $PbB = 0.533 + 0.675\ ^{3}\ PbW$ | PbW and PbB in μmol/1<br>first morning flush | Moore, et al. 1977 |
| $PbB = 0.304 + 1.036\ ^{3}\ PbW$ | running sample | |
| $PbB = 9.62 + 1.74 \log PbW$ | PbW in μg/1 PbB in μg/100ml<br>first morning flush | Lauwerys, et al. 1977 |
| $PbB = 0.8 + 0.19\ PbW$ | PbW and PbB in μmol/1<br>first morning flush | Moore, 1977b |
| $PbB = 0.8 + 0.53\ PbW$ | full flush (paired samples) | |
| $PbB = 19.6 + 7.2\ PbW$ | PbW in ppm, PbB in μg/100ml<br>first morning flush | Elwood, et al. 1976 |
| $PbB = 20.7 + 12.6\ PbW$ | As above.<br>Re-evaluated data | Beattie, et al. 1976 |

*Source: Berlin, et al. 1978

## TABLE 2

### Increment in PbB for an Increase of 100 μg/1 in PbW
(for Concentrations around 100 μg/1)*

| Increment in PbB | Remarks | Reference |
|---|---|---|
| 1.3 μg/100ml | For running sample (linear interpolation) 20-1040 μg/1 PbW | De Graeve, et al. 1975 |
| 1.2 μg/100ml | First flush (linear interpolation) 10-250 μg/1 PbW | Beattie, et al. 1972 |
| 3.4 μg/100ml | For running sample (linear interpolation) 10-250 μg/1 PbW | Covell, 1975 |
| 3.3 μg/100ml | For first flush (linear interpolation) 35-350 μg/1 PbW | Addis, et al. 1974 |
| 1.8 μg/100ml | Using the linear equation derived by the authors | Addis, et al. 1974 |
| 2.0 μg/100ml | Using the linear equation derived by the author for running water samples. | Moore, 1977a |
| 6.0 μg/100ml | Using the non-linear equation derived by the authors for running water samples. | Moore, et al. 1977 |
| 3.9 μg/100ml | Using the non-linear equation derived by the authors for first morning flush. | Moore, et al. 1977 |
| 0.83 μg/100ml | Using the log equation derived by the authors | Lauwerys, et al. 1977 |
|  | In view of the low PbW value, the extrapolation is uncertain. | Vos, et al. 1977 |

TABLE 2 (Continued)

| Increment in PbB | Remarks | Reference |
|---|---|---|
| 1.9 µg/100ml | Using the linear equation derived by the authors for morning flush | Moore, et al. 1977 |
| 5.3 µg/100ml | Using the linear equation derived by the authors for full flush | Moore, et al. 1977 |
| 0.72 µg/100ml | Using the linear equation derived by the authors for morning flush. | Elwood, et al. 1976 |
| 1.3 µg/100ml | Using the re-evaluated linear equation derived by the authors for morning flush. | Beattie, et al. 1976 |

*Source: Berlin, et al. 1978

the domestic supply than the population at large. In that regard, the only comparable population was 70 pregnant female subjects in the study of Hubermont, et al. (1978) cited in the CEC document as Lauwreys, et al. (1977).

In summary, of the studies cited in the CEC document, most weight should probably be given to the Moore, et al. (1977a) citation, on the basis of large numbers of samples of water and study subjects, and to the Hubermont, et al. (1978) study on the basis of a substantial number of subjects which were probably partaking of more of the domestic water supply than other sub-classes by virtue of pregnancy and sex.

So far as the actual calculations in Table 2 are concerned, there is one error. The CEC document calculates that the equation of Hubermont, et al. (1978) (cited as Lauwreys, et al. 1977) would predict that PbW at 100 μg/l would result in a PbB contribution of 0.83 μg/dl. The error is obvious. In the equation, the PbB contribution of water is given by PbB = 1.74 log PbW. In fact, 0.83 = 1.74 log 3, not 1.74 log 100. The correct calculation is PbB = 1.74 X 2 = 3.48, since log 100 = 2.

Of the 13 estimates of PbB vs. PbW in Table 2, only 5 could be verified. These were Addis, et al. (1974) (interpolation), Addis, et al. (1974) using authors' equation, Moore (1977a) using author's equation, Beattie, et al. (1976) using author's equation, and Moore, et al. (1977), non-linear morning flush. Of the remaining nine, one was miscalculated by CEC and the remaining eight could not be verified by this author because the paper was unavailable (Covell, 1975; Elwood, 1976), or because the necessary data were not in the paper (De Graeve, et al. 1975; Moore, et al. 1977 using non-linear equation for running water; Moore, et al. 1977 using linear equation for morning flush and running water calculations), or because it was not possible to see how CEC made an interpolation from the data cited (Beattie, et al. 1972).

In summary, the two most credible studies among the nine actually scrutinized in this addendum were the very ones utilized in the criterion document for lead. Of the two reviewed by the CEC but not examined at the time of this writing (Covell, 1975; Elwood, 1976), one was reviewed prior to development of the criterion document and rejected on the basis of the seemingly inappropriate use of a linear regression model (see "Contributions of Lead from Diet vs. Air to PbB" in the Pharmacokinetics section). It is therefore concluded that information provided by CEC does not alter the evaluations made in the criterion document.

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